Questions and Answers on Current Good Manufacturing Practice Requirements | Control of Components and Drug Product Containers and Closures

1. Do the CGMP regulations permit the destruction of an internal quality assurance audit report once the corrective action has been completed?

The CGMP regulations (21 CFR parts 210 and 211) for finished pharmaceutical manufacturing do not specifically address the requirement to conduct, or to keep records of, internal quality assurance audits. If the report in question was from a routine audit to verify that the firm's quality system is operating as intended, then it would be acceptable if the firm elected to discard the report once all corrections have been verified.

However, any documentation of corrective action as a result of such an audit would have to be retained (see §§ 211.180 and 211.188). For example, if a routine internal audit finds a problem with a mixing step and the outcome is a change in mixing time, all affected procedures, including the master production record, are to reflect the necessary changes, and such records are subject to FDA inspection as usual. Any investigation into the impact this problem had on related batches is to be retained and also made available for inspection by FDA (see § 211.192).

In addition, any reports of investigations or evaluations prepared in response to, for example, a product complaint (§ 211.198), vendor qualification (§ 211.84), periodic review of records and data (§ 211.180(e)), and a failure investigation (§ 211.192) are not internal audits as discussed above. Such records are subject to FDA inspection and must be retained for at least the time specified in the CGMP regulations (see § 211.180).

References:

21 CFR 211.84: Testing and approval/rejection of components, drug product containers, and closures
21 CFR 211.180: General requirements
21 CFR 211.188: Batch production and control records
21 CFR 211.192: Production record review
21 CFR 211.198: Complaint files
Preamble to the Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding regulations (43 FR 45015, paragraph 4, Sept 29, 1978)
Compliance Policy Guide Sec. 130.300 FDA Access to Results of Quality Assurance Program Audits and Inspections (CPG 7151.02)

2. Can containers, closures, and packaging materials be sampled for receipt examination in the warehouse?

Yes. Generally, we believe that sampling in a typical drug manufacturing facility warehouse would not represent a risk to the container or closure or affect the integrity of the sample results. But whether the act of collecting a sample in the warehouse violates the CGMP requirement that containers "be opened, sampled, and sealed in a manner designed to prevent contamination of their contents..." will depend on the purported quality characteristics of the material under sample and the warehouse environment. For containers or closures purporting to be sterile or depyrogenated, sampling should be under conditions equivalent to the purported quality of the material: a warehouse environment would not suffice (see 21 CFR 211.94 and 211.113(b)). This is to preserve the fitness for use of the remaining containers or closures as well as to ensure sample integrity, if they are to be examined for microbial contamination. At a minimum, any sampling should be performed in a manner to limit exposure to the environment during and after the time samples are removed (i.e., wiping outside surfaces, limiting time that the original package is open, and properly resealing the original package). Well-written and followed procedures are the critical elements.

Note that the CGMP regulations at 21 CFR 211.84 permit a manufacturer to release for use a shipment of containers or closures based on the supplier's certificate of analysis and a visual identification of the containers or closures. Once a supplier's reliability has been established by validation of their test results, a manufacturer could perform the visual examination entirely in the warehouse.

References:

21 CFR 211.84: Testing and approval or rejection of components, drug product containers, and closures
21 CFR 211.94: Drug product containers and closures
21 CFR 211.113(b): Control of microbiological contamination
21 CFR 211.122: Materials examination and usage criteria

3. A firm has multiple media fill failures. They conducted their media fills using TSB (tryptic soy broth) prepared by filtration through a 0.2 micron sterilizing filter. Investigation did not show any obvious causes. What could be the source of contamination?

A firm had multiple media fill failures. The media fill runs, simulating the filling process during production, were conducted inside an isolator. The firm used TSB (nonsterile bulk powder) from a commercial source and prepared the sterile solution by filtering through a 0.2 micron sterilizing filter. An investigation was launched to trace the source of contamination. The investigation was not successful in isolating or recovering the contaminating organism using conventional microbiological techniques, including the use of

selective (e.g., blood agar) and nonselective (e.g., TSB and tryptic soy agar) media, and examination under a microscope. The contaminant was eventually identified to be Acholeplasma laidlawii by using 16S rRNA gene sequence. The firm subsequently conducted studies to confirm the presence of Acholeplasma laidlawii in the lot of TSB used. Therefore, it was not a contaminant from the process, but from the media source.

Acholeplasma laidlawii belongs to an order of Mycoplasma. Mycoplasma contain only a cell membrane and have no cell wall. They are not susceptible to beta-lactams and do not take up Gram stain. Individual organisms are pleomorphic (assume various shapes from cocci to rods to filaments), varying in size from 0.2 to 0.3 microns or smaller. It has been shown that Acholeplasma laidlawii is capable of penetrating a 0.2 micron filter, but is retained by a 0.1 micron filter (see Sundaram, Eisenhuth, et al. 1999). Acholeplasma laidlawii is known to be associated with animal-derived material, and microbiological media is often from animal sources. Environmental monitoring of Mycoplasma requires selective media (PPLO broth or agar).

Resolution:

For now, this firm has decided to filter prepared TSB, for use in media fills, through a 0.1 micron filter (note: we do not expect or require firms to routinely use 0.1 micron filters for media preparation). In the future, the firm will use sterile, irradiated TSB when it becomes available from a commercial supplier. (Firm's autoclave is too small to permit processing of TSB for media fills, so this was not a viable option.) The firm will continue monitoring for Mycoplasma and has revalidated their cleaning procedure to verify its removal. In this case, a thorough investigation by the firm led to a determination of the cause of the failure and an appropriate corrective action.

References:

21 CFR 211.113: Control of microbiological contamination
21 CFR 211.72: Filters
21 CFR 211.84(d)(6): Testing and approval or rejection of components, drug product container, and closures
Sundaram, S, J Eisenhuth, G Howard, and H Brandwein, 1999, Application of Membrane Filtration for Removal of Diminutive Bioburden Organisms in Pharmaceutical Products and Processes, PDA J Pharm Sci Technol, 53(4):186–201
Kong, F, G James, S Gordon, A Zekynski, and GL Gilbert, 2001, Species-Specific PCR for Identification of Common Contaminant Mollicutes in Cell Culture, Appl Environ Microbiol, 67(7):3195–3200
Murray, P, E Baron, M Pfaller, F Tenover, and R Yolken, 1995, Manual of Clinical Microbiology, 6th ed., Washington, DC: ASM Press
Date: 5/18/2005

4. How many containers of each component from each shipment must a firm sample and test to comply with the CGMP regulations for identity testing? Do the CGMP regulations permit the identity test on a pooled, or composite, sample of multiple containers?

The CGMP regulations address component sampling and testing primarily at 21 CFR 211.84. These regulations require representative samples of each shipment of each lot of active and inactive component (or raw materials) to be tested to confirm the identity of the component as labeled prior to release for use in drug product manufacturing. The regulations acknowledge that more than one test may be needed to ascertain a component's identity. For the purpose of this answer, a component's identity is its chemical structure and its physical form (e.g., polymorph, solvate, and appearance) including, if appropriate, its stereochemistry or immunochemistry. (See also ICH guidances for industry Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances and Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.)

The CGMP regulations do not specify the number of containers to be sampled from each received shipment. However, § 211.84(b) establishes the principles to be followed in designing a sampling program for components. The requirements of this section can be summarized as follows:

Samples are to be representative of the shipment received.
The number of containers sampled as well as the amount of material sampled from each container is to be based on statistical criteria for component variability, confidence levels, and the degree of precision required.
The sample program takes into account the past quality history of the supplier.
The sample amount is to be sufficient for the necessary analysis and reserve samples.
The first three are most relevant to the question of how many containers to sample for identity testing, i.e., representative sampling, tolerance for variability and confidence required, and past history. (The amount needed for analysis and reserve can be readily met by sampling even one container, so the number of containers is not an important issue once the shipment's identity is verified.)

Unlike most component attributes, a component's identity is generally a discrete variable, i.e., the material in the container either is or is not what the label purports it to be. The component container's content might differ from what the container label states due to mistakes in filling and labeling by the supplier or repacker, or as a result of the substitution of a container's contents during distribution and warehousing before receipt by the drug product manufacturer. Using a wrong component in processing could result in a serious public health hazard. For these reasons, manufacturers need to develop an approach that provides a high degree of confidence that each container in each shipment contains the material purported by the label. (See also 21 CFR 211.160(b), which requires all sampling to be representative and scientifically sound.) The approach must account for the fact that the

material's identity must not vary from what is specified. The past quality history of a supplier and the scope of their operations is relevant to the chance for mistakes to occur under a supplier's control, but does not necessarily bear on what happens to a drug once it is outside the supplier's control.

How many containers of each component from each shipment must a firm sample and test to comply with the CGMP requirements for identity testing?

The regulation at § 211.84 requires that representative samples of each shipment of each lot shall be collected for testing. Some manufacturers have interpreted the CGMP regulations to require that each container in a shipment be sampled and tested for the attribute of identity. Testing samples from every container to determine identity may be valuable particularly for components purchased from distributors. (Analytical equipment and methods are readily available that permit rapid, nondestructive identification of material directly in containers in a warehouse area.) The CGMP regulations permit each drug product manufacturer to make its own decision as to the number of containers to sample, as long as the sampling plan is scientifically sound, leads to representative samples, and complies with the principles established at § 211.84(b). An important caveat applies with respect to § 211.84: samples are to be taken by the drug product manufacturer from containers after receipt (i.e., pre-shipment samples or so-called piggyback samples are generally not acceptable).

Do the CGMP regulations permit the identity test on a pooled, or composite, sample of multiple containers?

The CGMP regulations address the issue of sample compositing directly but only in the context of individual container sampling. Section 211.84(c)(4) explicitly prohibits compositing samples taken from the top, middle, and bottom of a single container when such stratified sampling is considered necessary (as might be the case when moisture content needs to be controlled, particularly when only a portion of a container may be used in a drug product batch). The preamble for § 211.84(c)(4) explains further that there "is no general prohibition... on compositing samples [from single containers] where such compositing would not mask subdivisions of the sample that do not meet specifications" (see 1978 preambleExternal Link Disclaimer, paragraph 231).

Testing individual samples from multiple containers provides a high level of assurance and is consistent with CGMP. Testing a composite sample for identity could satisfy the CGMP regulations (§§ 211.84 and 211.160) but only if a manufacturer demonstrates either that the detection of a single nonconforming container is not masked by compositing or that an additional test(s) routinely performed on the composite sample ensures that all containers sampled contain the same material. Thus, a purity assay on a composite sample prepared by mixing equal aliquots from each container may be acceptable provided such a test is sufficiently sensitive to reveal the presence of a single nonconforming container.

References:

Preamble to the Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding regulations (43 FR 45014, Sept 29, 1978)
21 CFR 211.82: Receipt and storage of untested components, drug product containers, and closures
21 CFR 211.84: Testing and approval or rejection of components, drug product containers, and closures
21 CFR 211.160: General requirements (Laboratory Controls)
FDA Guidance for Industry, 2000, ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances [Text or PDF]
FDA Guidance for Industry, 1999, ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products [PDF]

5. What methods of analysis are suitable for testing for melamine contamination in pharmaceutical components?

FDA recommends using a method demonstrated to be suitable for detecting melamine adulteration based on the manufacturer's risk assessment and prevention strategy. The manufacturer's selection of a sampling approach and test method sensitivity should address the possibility that (1) melamine might not be uniformly distributed in an at-risk component, or (2) that the source of intentional melamine contamination might be the starting material used to produce the at-risk component. The guidance for industry Pharmaceutical Components at Risk for Melamine Contamination provides a link to assay methods capable of detecting melamine at levels as low as 2.5ppm. These methods can detect melamine and cyanuric acid in complex matrices (protein materials) and, therefore, may be useful in developing test methods for other at-risk drug components. FDA also recognizes that a less sensitive method might also be appropriate for screening in certain cases.

References:

21 CFR part 211, subpart E: Control of Components and Drug Product Containers and Closures
FDA Guidance for Industry, 2009, Pharmaceutical Components at Risk for Melamine Contamination
Date: 12/17/2009

6. Does FDA require or recommend any special precautions or controls over the manufacturing of animal-derived drug ingredients to prevent contamination?

Yes, FDA requires that animal-derived ingredients be controlled in a manner to ensure that contamination does not occur, beginning with initial collection and handling of the animal-derived material through its processing and subsequent use in a finished pharmaceutical. See, for example, the Federal Food, Drug, and Cosmetic Act (FD&C Act) sections 501(a)(2)(A) and 501(a)(2)(B).

FDA has special concerns regarding the vulnerability of animal-derived ingredients to contamination by pathogenic agents (i.e., agents that can cause disease or illness in humans or other animals). As background, ingredients are also called components, and there are two categories of components used in finished pharmaceutical production: inactive ingredient (often called excipients) and active ingredient (often called active pharmaceutical ingredient (API)). For the purpose of this guidance, an animal-derived ingredient is a substance of animal origin used to manufacture a drug product. They are primarily derived from byproducts of food production and include extractions from certain animal material and milked animal fluids (e.g., venoms) and may even be human-derived. Products of animal cell cultures, including monoclonal antibodies and therapeutic proteins, are not considered animal-derived APIs for the purpose of this guidance. For additional information concerning biotechnology products, refer to ICH guidance for industry Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin. Ingredient manufacturers are responsible for the quality and safety of the material they produce for use in finished pharmaceuticals. Ingredients are drugs and drugs are required to conform with current good manufacturing practice (FD&C Act, section 501(a)(2)(B)). Finished pharmaceutical manufacturers are also responsible for their selection, qualification, and use of ingredients in finished pharmaceuticals (e.g., the CGMP regulations at 21 CFR part 211, subpart E). Ingredient and finished pharmaceutical manufacturers should fully understand the potential for pathogenic agent contamination beginning with the livestock processing establishment (LPE) and continuing through subsequent handling and processing, and establish stringent controls to prevent contamination. It is also essential that appropriate tests or examinations are developed and applied to detect contamination as part of any meaningful control program.

References:

FD&C Act, sections 501(a)(2)(A) and 501(a)(2)(B)
21 CFR part 211, subpart E: Control of Components and Drug Product Containers and Closures
FDA Guidance for Industry, 1998, ICH Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
Date: 1/27/2011

7. What are FDA's primary concerns about pathogenic agent contamination of animal-derived drug ingredients?

FDA is concerned about contamination of animal-derived ingredients by pathogenic agents during processing at the LPE, at a subsequent consolidator of animal material or raw material processing plant, or during the manufacturing process to create the final ingredient. One should assume that animal-derived materials will not only harbor but will often support growth of pathogens and accordingly should ensure appropriate control over the handling and processing of these materials. Current good manufacturing practice is to be followed in

handling such material to ensure that contamination does not occur that would affect the material's quality and purity, or that would be harmful when the product is administered to patients. Pathogenic agent contamination includes bacteria, molds, viruses, protozoa, parasites, and prions. Pathogenic agents can enter the manufacturing facility within the animal material and contaminate excipients, water, processing equipment, personnel, environment, or packaging. Contaminated drug ingredients present potential health risks that may affect various patient populations, including immune-compromised patients, as well as otherwise healthy people of all ages. An agent may be considered pathogenic if its presence represents a significant risk to patient safety. Factors affecting the pathogenic agent's ability to cause harm include the:

- Nature of the agent (pathogenicity, virulence)
- Amount of the pathogenic agent
- Type of manufacturing process and whether it affects the pathogenic agent's ability to survive
- Ability of the pathogenic agent to grow within the ingredient
- Type of drug product, and its route and length of administration
- Patient population for the drug product (including the most vulnerable patients who may take the drug).

Date: 1/27/2011

8. What manufacturing contamination risks are presented by the different pathogenic agents?

Manufacturing contamination risks presented by the different pathogenic agents can include the following: **Vegetative Bacteria** Vegetative bacteria are actively growing and reproducing bacteria. If there are no steps in the manufacturing process to kill vegetative bacteria, they can proliferate and accumulate during drug ingredient processing. **Toxin-Producing Microorganisms** Several genera and species of microorganisms are capable of producing toxins. Microbial toxins can be divided into two general groups: exotoxins and endotoxins. An exotoxin is a soluble protein excreted by a microorganism, including bacteria, fungi, algae, and protozoa. Exotoxins can include heat-stable toxins that remain active at temperatures as high as 100°C or heat-labile toxins that are readily inactivated by heat treatment. Exotoxins, especially heat-stable exotoxins, can remain in the ingredient throughout the manufacturing process and adversely affect patient health. An endotoxin is a component of the outer membrane of a Gram-negative bacterium. Unlike exotoxins, endotoxins are only released when the organisms are disrupted or destroyed. Endotoxins are heat- and chemical-resistant and, if injected, may induce reactions including febrile effect, hypotension, and shock. **Spore-Forming Bacteria** Spore-forming bacteria can be difficult to eliminate from the manufacturing environment because the spores may be extremely resistant to heat, freezing, extreme pH, desiccation, and chemicals. Spore-forming bacteria can produce exotoxins and can remain dormant without nutrients for extended periods. Spores can be resistant to harsh manufacturing processes that will kill vegetative bacteria. When dormant spores are reintroduced into an acceptable germination environment they

can become active reproductive vegetative cells. Once spores germinate and begin reproducing as vegetative cells, production of exotoxins can occur in a short period of time. **Fungi/Molds** Molds are a subset of fungi that reproduce by releasing spores into the air which, if they land on a moist nutrient source or animal tissue, can germinate. Some species of molds produce toxic byproducts called mycotoxins. Mycotoxins can accumulate in animal tissues, rendering the affected organs/tissues unfit for use as a source of starting material for the production of animal-derived drug ingredients. It is important to prevent molds from growing in drug ingredients and when feasible and valuable remove all molds that may contaminate such ingredients. Yeasts, another type of fungi, can also be pathogenic or cause spoilage of an ingredient. **Viruses** Although a virus can only multiply within its host, the inadvertent use of material from virus-infected animals or contact of the drug ingredient with virus-contaminated surfaces can transmit viral particles to patients. Virus survival rates differ based on virus type and variables associated with surface materials that become contaminated. On hard, nonporous surfaces, some virus species can survive and remain transmissible for days or weeks. The probability of an animal virus contaminating an animal-derived ingredient will depend on the viral load of the raw material (e.g., tissue, glands, blood) and the viral clearance capability of the drug ingredient manufacturing process. Both of these factors should be considered when assessing the risk of viral contamination of the ingredient. **Internal Animal Parasites** Transmission of internal parasites occurs from host to host through consumption of contaminated food or water. Parasites live and reproduce within the tissues and organs of infected hosts and are often excreted in feces. Government inspectors are trained to look for internal parasites and prevent unhealthy animals from entering the food supply. Animals deemed fit for food consumption are inspected and certified as healthy. **Prions** Protection from prion contamination includes obtaining bovine meat and meat byproducts from animals not infected with bovine spongiform encephalopathy and protecting against contamination of product with high-risk tissues, especially brain and spinal cord tissue. Drug manufacturers importing bovine material into the United States should be familiar with and adhere to all import eligibility requirements and government regulations pertaining to food and drugs. It is important that farms, slaughterhouses, and renderers observe government regulations prohibiting the use of unhealthy animals in the food supply. Animals deemed fit for food consumption are normally inspected and certified as healthy in many countries.

Date: 1/27/2011

9. What are some ways to minimize pathogenic agent contamination in incoming animal-derived raw material?

The drug component and finished product CGMP guidances and regulations emphasize prevention of problems and avoidance of contamination rather than final testing or examination alone. In other words, control strategies that prevent contamination are central to CGMP, while control strategies based on testing alone do not comply with CGMP regulations. Raw materials from animals can have microbial pathogen health risks based on country of origin, LPE processing, transportation, and manufacturing processing. Under the

right circumstances, raw material from animals can provide a suitable (e.g., nutrient-rich) environment for bacteria and mold to proliferate, or for viruses and other pathogenic agents to remain infective. If undetected contaminated raw material enters the manufacturing process, it can remain pathogenic in the product and a hazard to the consumer. The manufacturing conditions used in most ingredient manufacturing processes are often insufficient to eliminate all pathogenic agents from the ingredient. Methods of minimizing contamination of raw material with pathogenic agents may include the following:

- Animal source

When animal-derived material is used, it is important that it be derived from healthy, disease-free animals. The occurrence of pathogens can vary greatly among different animal species. Ingredient manufacturers should understand the pathogenic risks associated with different animal species and with different organs, glands, or tissues within species. Drug ingredient manufacturers should be aware that even healthy animals can be reservoirs for pathogenic agents and improper handling can spread contamination. If improperly handled, microbial contamination can transfer to uncontaminated tissues and cause contamination.

Ensuring the health of U.S. livestock is the responsibility of many Federal agencies, most of which are part of the U.S. Department of Agriculture (USDA). Animal-health and food-safety regulations are detailed in titles 9 and 21 of the Code of Federal Regulations. Animal health authorities in each State develop regulations that are consistent with the Federal agencies and are responsible for monitoring and controlling diseases in the State's domestic livestock and poultry. State inspectors ensure compliance by companies with individual State standards as well as with Federal meat and poultry inspection statutes. States assist in controlling diseases through inspections, testing, vaccinations, treatments, quarantines, and other activities.

Awareness of the conditions of control and monitoring of source animals will aid in determining which animals and animal parts are appropriate for drug product manufacturing.

- LPE

Ingredient manufacturers should consider auditing the LPEs supplying raw materials to them and ensure their compliance with all Federal and State government regulations. It is recommended that manufacturers develop standard operating procedures and define sanitation requirements of raw materials immediately after butchering, including, for example, the following:

  - Chilling requirements, if indicated, including temperature ranges and how soon after butchering chilling should begin
  - Chemical preservation methods, if indicated, including types and concentrations of chemical preservatives used
  - Storage processes, including sanitization of containers and container type/material (e.g., stainless steel vs. food grade plastics)
  - Transportation criteria, including sanitization of containers, if different from storage

and temperature ranges

The overall contamination of carcasses with pathogens depends on not only the prevalence and numbers of the pathogens on the hair, skin, and in the intestinal tract of the animal, but is significantly affected by the degree of cross-contamination occurring from these sources during slaughter and processing (see USDA references, below, for additional information). FDA expects that manufacturers will establish appropriate specifications for bioburden in their in-coming raw materials.

References:

USDA Animal and Plant Health Inspection Service
USDA Animal and Plant Health Inspection Service, Import and Export
USDA Food Safety and Inspection Service, Parasites and Foodborne Illness Fact Sheet
Date: 1/27/2011

10. Are there control measures for minimizing pathogenic agent contamination in animal-derived drug ingredient manufacturing facilities? Yes, control measures may include the following:

Process control

Holding and processing times for animal-derived material should be minimized to reduce the likelihood of microbial proliferation. The process qualification studies should include microbial sampling at multiple time points to evaluate the effects of time, temperature, and processing conditions on microbial growth. Routine microbial identification will provide valuable information regarding the types of organisms present in incoming material and throughout the manufacturing process. Processing conditions can then be adjusted to help control the number and types of organisms present during the manufacturing process. Spores and many bacteria can be removed by filtration when filtration or filtration cascade systems are possible. Usually filters with a pore size rating of 0.45 micron or smaller will remove spores and many bacteria from a preparation. Viruses and many toxins are heat labile so a heat treatment should be considered early in process development. Many purification and concentration systems may have antimicrobial effects. The timing and sequence location in the process along with appropriate holding and processing times may serve to optimize the antimicrobial effects of the processes.

Development of process monitoring tests and acceptance criteria should be established during the process development stage.

Facility and equipment controls

Facilities can also be reservoirs for pathogenic agents. Maintaining a facility within CGMP should include but not be limited to:

- Having adequately trained staff
- Using suitable quality water during manufacturing

- Having a facility design that minimizes the risk of cross-contamination
- Providing for proper storage of the ingredient

Cleaning procedures should include cleaning of facilities and equipment that ensures the removal of all raw materials between batches. Designing an effective cleaning program involves setting specific standards, understanding the facility's microbial environmental isolates, and selecting the right disinfecting agents to inactivate isolates that may be in the product or in the environment. Ingredient manufacturers should use sporicidal agents at appropriate intervals in the cleaning schedule to destroy bacterial and fungal spores.

References:

FDA Guidance for Industry, 2001, ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients
United States Pharmacopeia (USP) General Information Chapter <1072> Disinfectants and Antiseptics (USP33–NF 28 Reissue, 2010)
Wiley, JM, L Sherwood, and CJ Woolverton, 2008, Prescott, Harley and Klein's Microbiology, Boston: McGraw-Hill Higher Education.

11. What should drug manufacturers do to prevent formation of glass lamellae (glass fragments) in injectable drugs filled in small-volume glass vials?

Under certain conditions, glass vials can shed thin, flexible fragments called glass lamellae (Lachman, Lieberman, et al. 1986; Iacocca, Toltl, et al. 2010). These lamellae are shed from the interior surface of the glass container directly into the drug and are difficult to detect by visual inspection. Several drugs have been recalled due to this problem: epoetin alfa, methotrexate, hyaluronidase recombinant, and fluorouracil (see Enforcement Reports on FDA's Web Site). No adverse events to date have been reported nor can be directly attributed to this phenomenon. However, there is the potential for drugs administered intravenously that contain these fragments to cause embolic, thrombotic, and other vascular events (e.g., phlebitis); and, when administered subcutaneously, to lead to development of foreign body granuloma, local injection site reactions, and increased immunogenicity (Singh, Afonina, et al. 2010). The following conditions have been associated with a higher incidence of the formation of glass lamellae:

- Glass vials manufactured by a tubing process (and thus manufactured under higher heat). These vials are less resistant than molded glass vials and may shed lamellae more easily (Ennis, Pritchard, et al. 2001). The processing conditions used to manufacture glass vials can be designed to mitigate the potential for later delamination.
- Drug solutions formulated at high pH (alkaline) and with certain buffers. Common buffers associated with lamellae formation include citrate and tartrate (Sacha, et al. 2010).
- Length of time the drug product is exposed to the inner surface of the container. The

time duration has a direct correlation to the potential for glass lamellae formation to occur during the product shelf life (Lachman, Lieberman, et al. 1986).

- Drug products with room temperature storage requirements. Drugs stored at room temperature have a greater chance of glass lamellae formation than do products stored at colder temperatures (Iacocca and Allgeier 2007).
- Terminal sterilization has a significant effect on glass stability (Iacocca, Toltl, et al. 2010).

The referenced literature, below, includes recommended actions to help prevent the formation of glass lamellae. For example, for products "at risk," the vial surface alkalinity can be minimized by proper selection of glass composition (e.g., highly resistant, nonalkaline earth borosilicate glass), appropriate selection and qualification of vendors, and proper quality control of the incoming vials. Accordingly, FDA advises drug manufacturers of products to reexamine their supplier quality management program with the glass vial manufacturers to ensure that this phenomenon is not occurring. Further, the Agency reminds finished drug product manufacturers that CGMP regulations require that drug containers not be reactive or additive so as to alter the safety or quality of the drug. See 21 CFR 211.94; Rx-360's Web siteExternal Link Disclaimer, which has commented on the issue of delamination; and deviation reporting regulations for field alert reports (21 CFR 314.81) and biological product deviation reports (21 CFR 600.14).

References:

Lachman, L, H Lieberman, and J Kanig, 1986, The Theory and Practice of Industrial Pharmacy, 3rd ed., Philadelphia: Lippincott Williams & Wilkins, 645–649, 796–798

Iacocca, RG, N Toltl, et al., 2010, Factors Affecting the Chemical Durability of Glass Used in the Pharmaceutical Industry, AAPS Pharm Sci Tech, DOI:10.1208/s12249-010-9506-9

Singh SK, N Afonina, et al., 2010, An Industry Perspective on the Monitoring of Subvisible Particles as a Quality Attribute for Protein Therapeutics, J Pharm Sci, 99(8):3302–3321

Ennis RD, R Pritchard, et al., 2001, Glass Vials for Small Volume Parenterals: Influence of Drug and Manufacturing Process on Glass Delamination, Pharm Dev and Tech, 6(3):393–405

Sacha, G., et al., 2010, Practical Fundamentals of Glass, Rubber, and Plastic Sterile Packaging Systems, Pharm Dev and Tech, 15(1):6–34

Iacocca, RG, and M Allgeier, 2007, Corrosive Attack of Glass by a Pharmaceutical Compound, J Mater Sci, 42:801–811

21 CFR 211.94: Drug product containers and closures

21 CFR 314.81: Other postmarketing reports

21 CFR 600.14: Reporting of biological product deviations by licensed manufacturers

Date: 3/25/2011

12. Are there any special processing or handling concerns for flexible intravenous (IV) solution bags?

Yes, due to their soft and flexible design, IV solution bags can be easily damaged if not handled properly during processing and labeling. A damaged IV solution bag may not protect the contents from exposure to microbiological contamination as intended. Detection of a

damaged IV solution bag by leaks or by examination of the bag may not be possible. In fact, a microscopic defect may not be evident until microbiological contamination becomes visible, which is too late. Prevention of this potentially serious problem is important. FDA is aware of product recalls where IV products in flexible plastic bags were exposed to rough surfaces or sharp objects during labeling, creating microscopic punctures or weakening the bag surfaces. When a compromised IV solution bag is filled with liquid and expands as intended, holes may form at the weak points, leading to a loss of sterility or assurance of sterility.

Manufacturers are reminded that drug product containers and closures must be handled and stored in a manner to prevent contamination (see 21 CFR 211.80(b) and also 211.94).

References:

21 CFR 211.80(b): General requirements
21 CFR 211.94: Drug product containers and closures
Date: 7/5/2011

13. What can IV drug manufacturers do to help prevent the loss of sterility due to compromised IV solution bag integrity during labeling?

The risk of loss of sterility during labeling can be reduced through the use of nonimpression printing devices for labeling. If a manufacturer uses labeling equipment to apply a label on an IV solution bag and that labeling equipment makes an impression on the IV bag, procedures should be in place to inspect the labeling equipment regularly, particularly after any maintenance is performed. Manufacturing equipment must not have any rough or sharp surfaces that will create punctures or areas of weakness in the IV solution bags. Prevention is important: damaged IV bags may elude detection by standard examinations and tests, including checks for leaks. Manufacturers are reminded that equipment maintenance and cleaning must be appropriate to prevent malfunctions or contamination that would alter the quality or purity of a drug product (see 21 CFR 211.67).

Additional information: FDA Guidances

- Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice
- Container Closure Systems for Packaging Human Drugs and Biologics

References:

21 CFR part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals
21 CFR 211.22: Responsibilities of quality control unit
21 CFR 211.80: General requirements (for the control of components and containers)
21 CFR 211.94: Drug product containers and closures
21 CFR 211.67: Equipment cleaning and maintenance

21 CFR 211.100: Written procedures; deviations
Recall announcementsExternal Link Disclaimer FDA Warning LettersExternal Link Disclaimer
Date: 7/5/2011

14. Must each batch of a United States Pharmacopeia (USP)-grade API be tested using the analytical procedures specified in the USP monograph?

No; however, in the event of a dispute, the compendial method is considered conclusive (see USP reference, below). Section 201(g) of the FD&C Act includes "articles intended for use as a component" of a finished drug product, including APIs (or drug substances), under its definition of a drug, and section 501(b) requires a drug recognized in USP to meet the standards of strength, quality, and purity in the official monograph or to be clearly labeled to designate how it differs from USP standards. Although each batch of a compendial article must conform to the monograph specifications/acceptance criteria, the analytical procedures used to show conformance may differ from official USP methods if the alternative methods are fully validated, suitable for use, and give equivalent or better results than the official USP method. All APIs must also be manufactured in compliance with CGMP as stated in section 501(a)(2)(B) of the FD&C Act.

References:

FD&C Act Chapter V: Drugs and Devices
USP 38–National Formulary (NF) 33 (2015) General Notices, Section 6.30
Date: 6/9/2015

15. Who is responsible for analytically testing APIs to ensure they comply with their specifications and with USP requirements, if any?

API manufacturers perform analytical testing on APIs to confirm that they meet all applicable specifications established for release. Finished drug product manufacturers ensure that APIs used in their products meet all of their established specifications and—for compendial APIs—meet USP requirements. Additional information is provided below.

API Manufacturer Responsibilities Section 501(a)(2)(B) of the FD&C Act requires all drugs (including APIs) to be manufactured in compliance with CGMP. FDA therefore expects API manufacturers to follow the recommendations in ICH guidance for industry Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. API labeling supplied by the API manufacturer includes a certificate of analysis (COA). Section 11.4 of ICH Q7 recommends that the API manufacturer's COA should include, as applicable, the API's name, grade, batch/lot number, date of release, and a list of "each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained . . . ." For example, for a compendial-grade API, the COA should identify the compendial tests that were performed (as well as customer-specified tests, if any) and the test results. If a compendial-grade API differs from a USP standard of strength, quality, or purity, that difference should be clearly declared on the label.

Finished Drug Product Manufacturer Responsibilities In the CGMP regulations for finished

pharmaceuticals, 21 CFR 211.80 states that "[T]here shall be written procedures describing in sufficient detail the . . . testing . . . of [finished drug product] components . . . ." Additionally, 21 CFR 211.84(d)(2) states that "[E]ach component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals." Therefore, if the finished drug product manufacturer accepts the test results from an API supplier's COA rather than performing the tests itself (other than for identity, which the manufacturer is required to perform), the manufacturer must validate the API supplier's reliability. This validation procedure is established by the finished drug product manufacturer and should be consistent with the principles of CGMP and risk management. The finished drug product manufacturer should also ensure that compendial-grade APIs comply with compendial specifications, either by testing the APIs or by validating API suppliers' reliability, as described above.

References:

FD&C Act Chapter V: Drugs and Devices
21 CFR 211.80: General requirements
21 CFR 211.84: Testing and approval or rejection of components, drug product containers and closures
FDA Guidance for Industry, 2001, ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Date: 6/9/2015