Visual Inspection Discussion Points

QP Forum 2016
Q1: Discussion around assignment of criticality to defects found during visual inspection. How does this apply to Freeze Dried products?

- Defects are generally categorised into three categories: Critical, Major, Minor.
- Use Quality Risk Management approach to define the defect categories. This will be specific to the product you are manufacturing.
- QRM needs to take into account:
  - The type of product that is being made (e.g., Routes of Admin: IM IV)
  - The patient profile
Q1 contd.

• The process is the same whether it applied to liquid or freeze dried products. For freeze dried vials it is also recommended to take an appropriate sample and reconstitute the vial contents to facilitate full inspection.

• For defects from the market place, an evaluation needs to be carried out that assesses the medical impact of the defect taking into account the type of product and the patient profile.
What are the general levels of defects?

• Limits on levels of particulates should reflect your overall production process
  – It is important to:
    ▪ Know your process capabilities and your products
    ▪ Define quality requirements for your materials & primary packaging
      ➢ Particulates may be product specific
      ➢ There may be differences in particulate levels in glass vials that will differ depending on the vendor you use
      ➢ Effectiveness of vial washing can be variable & needs to be defined for your process
  – Cover these areas as part of new product development and product transfers activities
  – Review trending data from your visual inspection process & use it for continuous improvement
Q2 contd.

• Limits for defect levels for VI should be as tight as possible & be linked with the capability of your VI processes

• Limits typically observed in industry:
  o Critical Defects – 0% to 1%
  o Major Defects – 1 to 3%
  o Minor Defects – 3 – 5%

*Note: These should not be taken as acceptable or as guidelines for your specific application*
Q3: Are Regulatory authorities asking for separation of Inspection personnel from their operational unit?

• FDA has stated a clear expectation that the VI checks are done by people with no interest in the performance of the individual inspections.

• In general, authorities are looking for strong QA involvement in the performance of VI checks and separation of the inspection activities from the operational unit.

• FDA has issued citations for a low level of involvement by QA in the oversight of VI activities and where personnel performing checks reported to the operational unit.
Q4: Has anybody experienced difficulties with automated inspection validation and what are the regulatory citation trends relating to automated inspection?

• One participant indicated that they had problems with the shoulder area of the vial in validation, but they had been able to overcome the issue

• There is not a lot available in the public domain on regulatory citations related to visual inspection. The following slides have been assembled to reflect recent citations relating to particulates & VI:
Visual inspection of sterile finished product

Regulatory citations
Recent FDA Warning Letters

• 23/02/2016, to South Coast Specialty Compounding, Inc. (producer of sterile drugs)

“The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

Specifically, ….. during the walkthrough on 23/02 we observed the inspector (Pharmacist) visually inspecting Ascorbic acid in amber vials. There is no written procedure other than visual inspection procedure to test for particulate matter for finished sterile drug products stored in amber vials after non-sterile to sterile, lyophilization or sterilized process. The firm switched most of the clear vials to amber vials approximately xx ago.”
Recent FDA Warning Letters

• 04/01/2016 to Pharmedium Services, LLC (outsourcing facility headquarters)

“Laboratory controls do not include the establishment of scientifically sound and appropriate specifications designed to assure that components and drug product containers and closures and drug products conform to appropriate standards of identity, strength, quality and purity.

…. Your firm has also not documented specifications for each of your formulated drug products purporting to be sterile to include at a minimum the identity and strength of each active ingredient, a limit for visible particles, sterility and limit for bacterial endotoxins.”
Recent FDA Warning Letters

• 06/01/2016 to Wellcare Rx Investments (producer of sterile drugs)

“During a field examination of drug products at your facility I observed a vial of sterile human finished drug product Chlorpromazine HCL 25mg/ml …. with what looked like particles floating in the drug product.”

• 03/12/2016 to JCB Laboratories, LLC (outsourcing facility)

“There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically, we discovered a single vial of lot # 150518@2 of Betamethasone separated in the retain samples, that appears to have particles and low fill, and had no investigation written up on it. This lot was implicated in DEV-2015-286, which details a complaint with five patient illnesses.”
Recent FDA Warning Letters

• 29/12/2015 to Dougherty’s Pharmacy (producer of sterile drug products)

“Laboratory controls do not include the establishment of scientifically sound and appropriate specifications designed to assure that components and drug product containers and closures and drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically, Your firm’s product inspection process is deficient in that you do not perform 100% visual checks, against a contrasting background of your sterile liquid formulations prior to release. According to the “Compounding” Manager, about xx of the finished products are visually inspected. Additionally, your firm has not established a written procedure for performing visual checks within products.”
Recent FDA Recalls

• 25/04/2016 Fresenius Kabi recalls one lot of Sensorcaine®-MPF (bupivacaine HCl) injection, USP …. 30 mL fill in a 30 mL vial …. due to visible particulate matter characterized as glass observed by the company during inspection of reserve samples.

  Administration of a solution containing glass particulate matter by the epidural or retrobulbar (behind the eyeball) route may result in inflammation and injury, or cause blockage of vasculature around the eye or emboli in the vasculature of eye nerves

• 13/04/2016 Hospira Inc., a Pfizer company, recalls one lot of 50% Magnesium Sulfate Injection, USP…. single-dose vials…. due to a confirmed customer complaint for the presence of particulate matter, within one single-dose fliptop vial.
Recent FDA Recalls

• **28/03/2016** B. Braun Medical Inc. of Irvine, CA recalls one lot of 5% Dextrose Injection USP… B. Braun recently identified an adverse quality trend in customer complaints reporting that some containers in lot J5J706 exhibited leakage and, in a few instances, visible particulate matter identified to be microbial growth.

• **18/03/2016** Hospira, Inc., a Pfizer company recalls one lot of 8.4% Sodium Bicarbonate Injection, USP… due to the presence of a particulate within a single–dose glass flitop vial.

• **09/03/2016** Teva Pharmaceuticals recalls one lot of amikacin sulfate injection USP 1 gram/4mL (250 mg/mL) vials due to the potential presence of particulate matter identified as glass in one vial.
Recent EU Statements of Non-compliance with GMP

- **02/02/2016** Spanish Agency of Medicines and Medical Devices issued a Statement of non-compliance with GMP to Farma Mediterrania, S.L., site address in Spain
  
  A critical deficiency: Although a visual inspection of injectable medicinal products reveals a high number of critical quality defects (the presence of visible particles) no deviations are opened and it is not investigated.

- **03/12/2014** French National Agency for Medicines and Health Products Safety issued a Statement of non-compliance with GMP to Medreich Limited – Unit V, site address in India

  29 deficiencies have been classified as “major”. Among them 9 were related to production (sterile and non-sterile products) including risk of cross-contamination, poor visual inspection process handling, poor in-process control handling (weight of vials, weight of tablets and hard capsules), poor handling of broken vials issues.
Contact

A | Suite 2, Stafford House, Strand Road, Portmarnock, Co. Dublin, Ireland
P | +353 (0)1 846 47 42
F | +353 (0)1 846 4898
E | info@mcgeepharma.com
W | www.mcgeepharma.com