NEW ENGLAND PDA NEWSLETTER

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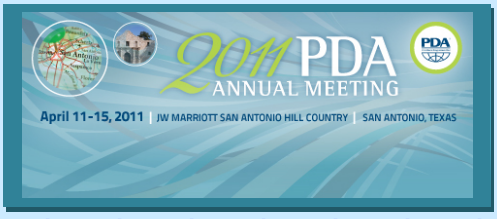
Connecting People, Science and Regulation

Upcoming Events



PDA Course:
Global Regulations and Standards: Influences on Cold Chain Distribution, Packaging Testing and Transport Systems

PDA #122
|ACPE #0116-0000-11-122-L04-P |
1.2 CEUs
Location: PDA Training and Research Institute in Bethesda, MD
Date: March 3 - 4, 2011
Duration: 2 Days, 8:30 a.m. – 4:00 p.m.

2011 PDA/FDA Atypical Actives Workshop

Coming Together to Develop Solutions
March 9-10, 2011 | Hyatt Regency Bethesda | Bethesda, Maryland

Handling Investigations of Extraneous Matter Contamination

By Roland Bizanek, PhD, MPD
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1. Introduction

Recently several pharmaceutical manufacturers received warning letters and Form 483's from the FDA due to deficiencies in investigating contamination with particulate or extraneous matter.[1] While this is of specific importance in injectable drug product, it must not be ignored in oral drug product or drug substance. Any drug contaminated with extraneous matter or drug manufactured under conditions where it may have been contaminated is considered adulterated according to the Federal Food, Drug, and Cosmetic Act (FD&C Act) Section 501 (a)(1) or (a)(2)(A).[2] The following approach outlines the steps in investigating potential contamination with extraneous matter in drug product or drug substance.

2. Investigation

A thorough, systematic investigation must be conducted and documented any time a potential contamination of a batch of drug product or drug substance is suspected through either observation or testing during manufacturing or as part of a customer complaint. This investigation process needs to be documented in a Standard Operating Procedure (SOP)[3], all applicable personnel must be trained on this SOP[4], and the internal audit and management review process must verify that such SOP is being followed[5]. The following steps of the investigation can be conducted in sequential or parallel fashion and in most cases, some of these steps may have to be repeated as new information is obtain during the investigation.

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Review of Inspection Methods to find Particulate Matter

By Eileen M. Scanlon

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Dr. Bizanek's thoughtful article Handling Investigations of Extraneous Matter Contamination touches on a number of important considerations after particulate contamination has been identified in parenteral products. Mainly the actions that must be taken once particulate contaminated products have been identified. This article talks about the various methods of inspection to identify the products containing particulates.

Parenteral products are required by various guidelines and Regulatory agencies to be 100% inspected before being sold. Parenteral inspection can be accomplished in 3 different ways:

- Manual Inspection
- Semi-Automatic Inspection
- Fully Automatic Inspection including Container Closure Integrity Testing

Manual Inspection

Manual inspection is the first level and it considered to be the benchmark for all other inspection methods. This method , outlined in the USP, is a human operator examining each vial, ampule, syringe or bottle under controlled lighting and alternatively against a white and white background. The emphasis in the Compendia is on the removal of particulate matter from liquids. In practice, this inspection is generally also used for cap/crimp defects and for cracks and other glassware defects. Additionally, in syringes, it can be used to confirm correct placement of plunger, and needle assembly. These other defects are often called "cosmetic" defects but in reality can pose an equally serious risk to patient health as a defective cap/crimp or glass crack can breach product sterility.

Manual Inspection is also used for lyophilized products. Finding particulates in lyo products after lyophilization is more problematic because only the top, bottom and sides of the lyo cake are available for visual inspection. It is very easy for foreign contamination to be trapped inside the lyophilized cake. There are machines and methodology available for inspecting lyo products while they are still liquids before the lyophilization process but this requires inspection in the Clean room while the vials are only partially sealed. This has been discussed extensively in various PDA forums but has not been adopted in significant numbers by the industry. This is likely to be because of the further potential contamination during this inspection process. After lyophilization, using visual inspection , it is possible to find particulate matter on the top, sides or bottom and to find other defects must as "meltback" and partially lyophilized cakes. There are technologies available to find defects inside the lyo cake such as X ray but they have not yet been widely adopted.

Up until now, there has been little formal regulatory guidance in some very important aspects of Manual Inspection such as amount of light needed; whether or not magnification should be employed and more importantly how long each product should be inspected for. The PDA under the guidance of Mr. John Shabushnig of Pfizer has helped the pharmaceutical industry formulate approximate industry standards but these are not enforceable and there have been wide variations in practice. However, Guidelines are being worked on and are expected to be issued shortly. **Continued on page 6.**

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2.2 Confirm Contamination

The first crucial step in an investigation of batch contamination due to foreign or extraneous matter is to confirm that the batch was in fact contaminated with such material. One of the most common pitfalls is to test for the absence of a contaminant in the product. A negative result of such test is not an indication that no contamination occurred, because the contaminant is usually not uniformly distributed throughout the batch. In special circumstances, an inspection of the whole batch rather than a sample could be used to determine the degree of contamination, e.g., visual inspection of prefilled syringes or sifting of solid drug substance.

Another point to consider is whether the potential contaminant is actually foreign to the product and process. In some cases, drug substance and/or excipients could precipitate in a drug product solution. Such occurrence would not be considered a contamination; however, the impact of particulate in the solution needs to be assessed and a thorough investigation needs to be completed.

2.3 Identify Affected Batches

Once the contamination has been confirmed, it is critical to ascertain the affected batches and to place these on quarantine or consider batches already in distribution to be recalled. In many incidents this part of the investigation has been deficient leading to subsequent observations during regulatory inspections and/or further regulatory actions, e.g., warning letter.

This assessment needs to be repeated, once a (potential) root cause(s) has been identified and documented in the investigation. Based on the root cause(s) analysis additional batches, which were previously not identified, may need to be included in the impact assessment. This could lead to the potential assessment of other products. A rationale of the determination of the affected batches should be documented in the investigation.

2.4 Identify Contaminant

Once a sample of the possible contaminant has been obtained, any reasonable effort should be conducted to identify the material. This will be helpful in determine the root cause(s) of the contamination, the potential impact on the product, the possibility of any reprocess or rework of the affected batches and their disposition.

If the identity of the contaminant cannot be determined, the affected batches should be rejected as the assessment of the toxicological impact cannot be conducted. Without this assessment the risk to the patient cannot be determined adequately.

2.5 Assess Toxicological Impact

In the next step, the toxicological impact on the product needs to be assessed based on the identity of the contaminant, an estimate of the amount of the contaminant in the batch, the batch size of the product, and the daily maximum dosage used on the resulting drug product. This assessment should be conducted in conjunction with toxicologists and physicians to adequately assess the risk of this contaminant to the patient. If the contaminant has been characterized as highly objectionable, e.g., because it is a toxin, the affected batches should not be considered to be reprocessed or rework and rather be rejected.

While the affected batch(es) could be rejected, the investigation needs to be completed to determine adequately the (potential) root cause(s) and any corrective and preventive actions

2.6 Determine (Potential) Root Cause(s)

During the root cause(s) analysis of the investigation, all aspects of the product and process should be evaluated, e.g., manufacturing process of the product, components of the product including packaging components, environmental controls during manufacturing including packaging, personnel.

As in all other investigations, sometimes a root cause(s) or potential root cause(s) cannot be determined. It is critical in such cases to continue the investigation until all avenues are exhausted and document thoroughly the results of such root cause(s) analysis in the investigation.

Additionally, it is a common pitfall to stop the investigation once a root cause(s) has been identified. This practice is based on the wrong assumption that the incident is based on just one definite root cause(s). Even if the "smoking gun" has been identified from the beginning of the investigation, a systematic root cause(s) analysis needs to be conducted and well documented.

2.7 Determine Correction

Correction refers to the remediation process of the nonconforming material, which brings it back into compliance with applicable specifications and/or standards.

It is important that any affected batch is either reprocessed/reworked to remove the contaminant or rejected. In some cases, a reprocess or rework of the product is not feasible and the product needs to be rejected. If the identity of the contaminant cannot be determined, the product needs to be rejected

In specific cases, the continuation of the manufacturing process could remove the contaminant and a specific reprocess or rework may not be necessary, e.g., subsequent recrystallization of solid drug substance.

In any case, sufficient rationale should be documented in the investigation for the reprocess/rework procedure or the continuation of the manufacturing process (see above), which should include documented evidence that the contaminant has successfully been removed from the affected batch.

Keep in mind that if the manufacturing process has previously been validated, the reprocess/rework procedure has to be validated including justification of critical process parameters and determination of how many times a batch could be reprocessed/reworked

Furthermore, any applicable filing activities with the appropriate regulatory agencies in regards to the reprocess/rework procedures may need to be completed prior to distribution of the finished product.

2.8 Determine Corrective and Preventive Actions

Corrective action refers to any activity to eliminate the cause of a detected nonconformity or other undesirable situation. Preventive action refers to any activity to eliminate the cause of a potential nonconformity or other undesirable situation (which has not occurred yet).

Based on the completed root cause analysis corrective action(s) need to be determined and implemented. Further preventive action(s) may have been identified during the root cause analysis and need to be implemented as appropriate. While there may be more than one (potential) root cause identified, there might be more than one corrective and preventive actions identified. The effectiveness of the implemented corrective action(s) should be demonstrated and documented.

2.9 Approve Completed Investigation and Disposition Affected Batches

Finally, the completed investigation needs to be documented in appropriate form, reviewed and approved by appropriate personnel according the SOP governing investigations. This document should list all the results from the above steps and applicable rationale for the decision made by the firm. Based on the completed investigation the disposition of the affected batches needs to be rationalized and documented including any assessment of already distributed batches, which have been affected by the incident.

3. Conclusion

Recent developments in the regulatory environment warrants increased focus on investigation process for contamination incidents including the writing of such investigation reports. The investigation should follow a well established and systematic process documented in a detailed SOP. The outcome of this investigation, i.e., (potential) root cause(s) and impact assessment, any applicable data, and rationale for determining the affected batches and for any decisions made on the disposition of the affected batches needs to be well documented in the investigation report. Furthermore, the rationale for any applicable corrections, corrective and preventive actions needs to be documented. Such a systematic and well documented investigation will increase the assurance that the incident and subsequent decisions by the firm can be successfully defended during an inspection.

Trying to get Noticed??

We offer vendors, consultants, operating companies and other organizations the opportunity to promote themselves and also support the NE PDA Chapter by purchasing advertising in our newsletter. A **business-card size advertising opportunities in our newsletter; at a cost of $100 per newsletter and we have added new sizes and ad placements. Details are available at**

http://www.pda.org/MainMenuCategory/Chapters/New-England/Chapter-Resources_1.aspx

The newsletter has the following reach:

- **Our direct e-mail distribution reaches over 1,800 contacts throughout New England.**
- **Our membership includes people from manufacturing, research, QA, QC, engineering, contract manufacturers, consultants, and regulatory.**
- **We promote the newsletter at New England PDA's bi-monthly dinner meetings, often with company tours, which regularly attract 50-100 attendees.**
- **We post the newsletter on our chapter's website at Global PDA (www.pda.org), an organization that has over 10,000 members.**

Deadline	Publication Date
March 01, 2011	April 2011
July 01, 2011	August 2011
October 01, 2011	November 2011

If you are interested in advertising in the newsletter or need more information, please contact a NEPDA Board Member.

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Semi-Automatic Inspection

Semi-Automatic inspection machines have been widely used worldwide in the past 30 years to help make manual inspection more consistent and speed up this labor intensive operation. The concept of Semi-Automatic inspection is to relieve the operator of the necessity of handling the products to be inspected and at the same time improve inspection conditions by consistently presenting the products in the same orientation with optimized lighting and magnification. The operator still makes the accept or reject decision. Typical semi automatic inspection machines, such as the Seidenader V90-AVSB/60 , automatically feed in products from a turntable or previous process and transfer them onto transport rollers designed to the container size. For liquid filled products there is a pre-spin function that agitates the liquids, then the products are brought into the operator viewing area where there is intense light (typically Halogen light sources conveyed to the inspection area by fiber optics), 2X magnification and top and bottom mirrors to allow the operator to see all the possible defects. The inspector then makes an accept/reject decision and can utilize an automatic removal system for defects or manually remove them from the rollers. For prefilled syringes, the rollers are designed to

support the syringes and often the syringes are turned to allow them to be inspected needle up.

As in manual inspection, typically semi-automatic inspection is used for particulates in the liquids and also cap/crimp and glass defects in the rest of the product. It is also used to find defects in lyophilized products and similar to manual inspection , only the outside surfaces of the lyo cakes are inspected. It is generally agreed that semi-automatic inspection should be able to increase operator inspection productivity by about 300-400%, while increasing the quality and consistency of the inspection.

Fully Automatic Inspection

Fully Automatic Inspection takes the human inspector out of the inspection process completely. Fully automatic machines detect particulate matter in vials, ampules or syringes using sophisticated cameras or sensors (e.g., Seidenader camera systems and Eisai static division sensors). Each of these modalities require the liquid to be agitated prior to the inspection and the arrangement of lighting and other optical elements are critical to the performance. Fully automatic inspection systems are typically used in medium to high speed lines of over 100/upm. Fully Automatic machines can be just for particulate inspection where other inspections (closure and glass defects) are done either manually or semi-automatically but more commonly one machine does all aspects of inspection. For example, on a Seidenader Model VI Fully automatic inspection machine, there would be 2 or 3 camera stations doing particulate matter, 1 cap/crimp inspection station, 1 sidewall inspection station , 1 bottom inspection station and possibly camera stations dedicated to heel and should area inspection. For each camera station, there will be different rotations, different light configurations, different optical set ups and different number of cameras. Each camera station must optimize the capturing of images that then can be analyzed by vision processors to identify the defects. The vision processors make an accept/reject decision according to the pre-programmed parameters. A key component of fully automatic inspection is to be able to reliably locate defective vials without also rejecting acceptable products which is known as the False Reject Rate (FRR). High FRRs are generally unacceptable because of a decrease in yield.

Defect Limits & Defect Categorization:

No mater inspection method is used, it is critical to set **Defect or Action Limits**. This is an upper limit expressed as a percentage of the number of defects that can be found in a batch before an investigation is required or the entire batch is rejected. There is usually both an overall Defect Limit for all rejected units and specific Defect Limits for each category of rejects. Defect categorization can be done by the primary inspectors in either manual or semi-automatic inspection as they inspect, i.e., putting different types of defects into different boxes or all defects can be re-inspected and categorized at the re-inspection point. Fully Automatic inspection machines can have multiple exit channels for different types of rejects or all rejects can be re-inspected and categorized at that time.

Particulate rejects are generally classified into: Fibers; Glass Fragments; Metal pieces or others. Most particulates can be traced back to the manufacturing process. Of course, great care is taken to avoid particulate contamination but it does occur and complete inspection is the first step towards identification and action.

Conclusions:

The mandated 100% inspection of parenteral products can tell a manufacturer a great deal about the quality of their products. Thorough Inspection gives a parenteral manufacturer the tools needed to insure final product quality and to move onto the next steps to investigative and prevent the sources of particulate contamination as discussed in Dr. Bizanek's article.

Student Chapter News – An Update from PDA NE Scholarship Recipient Diane Moustafa

Dear Members of the PDA New England Chapter,

I would like to take this opportunity to thank you for acknowledging my motivation and drive in regards to my education.

In 2009 I was the first recipient of the transfer scholarship for students going from a community school to a four year school. Needless to say this scholarship helped my family tremendously. I am the mother of four and grandmother of three. Financially I could have never have paid for the tuition of the four year school.

I entered Boston University for the fall semester of 2009. Receiving this scholarship gave more motivation than words could ever say. I took the maximum credits I could take every semester. I will be graduating this May with my bachelor's degree in science. Yes, I did say this May. Your scholarship made this happen. I can honestly say that without this scholarship it would have taken me at least eight years instead of the two years.

I am now looking forward to graduate school. I have several options one being Harvard Extension. If I had not received the extra boost in confidence I received from getting the scholarship this could have never been possible. I am the very first person in my family to earn a college degree. I now have two of my children attending college. They said "if you can do it mom, I can do it." I am so very grateful for the opportunity you have given not just me but my children. They saw how much my education meant to me and are now fulfilling their dreams of having a degree.

I hope and pray you will continue to give this scholarship to other motivated students.

I have one more goal I would like to accomplish before I graduate BU. I would like to graduate with another student chapter in place at BU. I believe that any student who gets involved in a student chapter only benefits from the knowledge the PDA brings.

I would like to extend my gratitude by going to Middlesex Community College and talking with the students about the importance of PDA events and push all of them to apply for the wonderful opportunity that the transfer scholarship brings. Also I have spoken extensively with Connie Phillips at Boston University of the students doing a poster presentation at a dinner meeting.

Again, thank you so very much for everything you have given to me. My family and I truly appreciate the gift of this special scholarship.

Sincerely

Dianne Moustafa

Keep up the great work Diane! - Board of Directors, PDA New England Chapter