PDA
Update on Technical Reports, recent Projects
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**Quality Metrics Points to Consider / Quality Culture Survey/ Workshops 2013, 2014**
**Drug Shortage Workshop 2014 / Technical Report**
Scientific and Regulatory Affairs

PDA Journal of Pharmaceutical Science and Technology
Founded in 1947
Peer-reviewed
Published Bimonthly
Circulation of Over 10,000
Member Benefit

Regulatory Activities
- Prepare Regulatory Comments
- Strategic Planning
- Participate in Regulatory Authority Meetings
- Participate in PDA/PICS, PDA/FDA & PDA/EMA Meetings

Technical Reports
- Over 50 TRS in Pipeline
- Facilitate Technical Report Team (TRT) Meetings
- Review Technical Reports
- Administration and Editing Activities

PDA Workspace
- Technical Report Team Collaboration Space
- Advisory Board Balloting
- Document Management

TRI Course Material
- Develop PDA-Owned Courses
- Act as Course Instructors
- Plan Research Activities

Technical Report Team Management

Programs & Meetings
- Support
  - Agenda Content
  - Speaker Recommendations
  - IG Meetings

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Process to develop a PDA Tech Report

• Starting point:
  – Hot topic
  – General interest
  – Lack of guidance (high variability in execution)

• Written proposal: Problem/Scope statement

• Establish a Taskforce

• Decision by Advisory Board and PDA Board

• Execution (writing 1-6 years)

• Reviewing

• Approval

• Publication
Pre-execution phase

• To prepare the scope statement:
  – IGmeetings
  – Conferences
  – Surveys
  – Internal meetings
Members of Task Force

- PDA members
  - Pharma&Biopharm. Industry
  - Supplier/Technology Providers
  - Regulators
  - Academia

- Members are selected based on experience in the field
Selected Topics

• Previous Activities
  – Glass quality

• On-going Activities
  – Particulate Matter
  – Objectionable Organisms
  – Drug Shortage
Glass Quality

Crack

Location: General

Class: Critical
• PROBLEM STATEMENT

Over the past several years there have been a number of reports of glass quality issues, including defect and the formation of glass lamellae. Some of these have resulted in recalls.

There is a lack of clarity and consensus among purchasers (pharma manufacturers) and glass suppliers as to the cause and even the terminology of glass and glass defects.
Technical Report No. 43 (Revised 2013)
Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing: Covering Ampoules, Bottles, Cartridges, Syringes and Vials
Particulate Matter
Over the period of 2008 - 2012, particulate related issues have led to **22% of product recalls for injectable products**.

In 2007, the European Medicines Agency (EMA) performed an analysis of product quality defects reported in 2005 and that **6% of all product quality defects** were attributed to particulates.

Those particulate defects that resulted in a recall would have been classified as either a Class 2 or Class 3 (EU recall).

Between January 2013 and June 2014, there were 42 drug alerts to the Medicines and Healthcare products Regulatory Agency (MHRA) Drug Alert web site, with **11 drug alerts relating to particulates**.

Those alerts reported in 2014 were all Class 2 and included metal particles (both Reckitt alerts), small white particles (Strides), fibre and glass particles (Actavis) and silicone fragments (Gilead).
Particulate Matter

2008-Present
Increasing Numbers of Recalls Due to Visible Particulates

PDA Initiate Task Force 2013

Workshops to Discuss with Stakeholders 2014

PDA Draft Points to Consider Document (Q3 2014)
Key Discussion: Points/Themes

- We share a common goal of no particulates in parenteral products, but are working towards a practical non-zero limit based on patient risk.

Limitations and Capability of Current Inspection Methods and Technology
- Will recently published USP <790> change FDA practice upon inspection? Will the new standard have potential to penalize more sensitive inspection methods?
- If agreement is reached to allow “some” visible particles, what should the AQL be? How does choosing this limit incentivize good inspection practices?

Are all particles created equal?
- Should foreign matter (e.g. hair, skin, wood) be treated the same as intrinsic or expected particles in terms of allowable numbers? Should all particles be treated equally? For example, cellulose on a stopper versus iron? How far do you really need to go to investigate a single occurrence or incident of a particle on a stopper?

Impact on Patients
- How does one ascertain the relative risk of injecting sterile inert particles in subcutaneous, intramuscular and intravenous tissues? What harm is the agency seeing to patients from particles? What are thoughts on risks unique to certain populations to protect the most critical patients?
Areas of Agreement

• Any use of AQL approach is contingent on “good” inspection process and QMS at the site. i.e. Validated inspection methods and equipment, proper operator training, appropriate QC oversight

• US 501(a) definition of “filth” still applies.
  – It is a misconception that larger particles pose greater patient risk than smaller particles. Clinical evidence suggests otherwise.
  – Firm must understand what particulates they are seeing (even if within the AQL) Recommend use of leading and lagging trend analysis of background and atypicals

• Suggest **trending of rejects** not just AQL samples
Areas of Agreement (cont.)

• Visible, sterile, inert particles for IM or SQ injections to the general patient population **pose an acceptable risk**.

• AQL of 0.65 per USP 790 is reasonable.

• **High risk populations** (e.g. Pediatric, route of administration, high volume IV under pressure) may need a tighter AQL.
  – “Intended Use” to determine patient population should be defined by the label
  – Off label uses not considered except in special cases such as a known, large pediatric use
Areas of Agreement (cont.)

- For particles that are primarily mechanical obstructions, the composition of a particle is not critical to clinical impact except for impact on sterility. (*discussion scope was for particles such as cellulose, metal or fiber and did not include particles with possible therapeutic or immunological impact such as agglomeration in protein products*)
  - **ID of particle very important** as a process control indicator. / may be surrogate for another issue.
  - **Recall “on one”** is to be determined in the context of mfg. history and complaint rate; **not automatic** for single particle found in a single unit alone.
Issues To be Discussed Further

• Are there high risk product types? Should AQL be set product by product? Perhaps could look at groups of products used by high risk patients
• How and when to revisit AQL in the future? To balance cost/benefit with patient risk
• USP <790> creates no new requirements on stability. What should be the appropriate steps to evaluate risk from particulates found over time?
• Spec of one particle per stopper is not acceptable but capability of component suppliers is limited. Quality should have a voice in procurement process to choose suppliers with high enough quality.
Recommendations and Next Steps

• Recommend placing **AQL in application specs** for new products.

• Recommend using **Annual Report to add USP AQL** for existing products but must do risk assessment before adding.

• May submit change via **CBE30 for a higher risk product** or if there is a limited capability to meet USP <790>.
“Objectionable” Organisms
Objectionable Organisms

Continuing issues of lack of consistent understanding of "objectionable"

PDA Initiate Task Force 2013

PDA Draft Technical Report (Q3 2014)
EXCLUSION OF OBJECTIONABLE MICROORGANISMS FROM NONSTERILE PHARMACEUTICALS, MEDICAL DEVICES AND COSMETICS

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Objectionable Organisms
Executive Summary

• The term “objectionable microorganism” is used in the GMP regulations of the United States and European Union and has been adopted in the regulations of several other countries.

• However, the term is not well defined, which often leads to disagreement about interpretations of the term and product disposition decisions made.

• This technical report contains information on how to mitigate the risk of microbiological contamination of nonsterile products, provides risk-based decision criteria for recommended levels and types of testing to be performed, offers references to suitable literature to identify microorganisms of concern, and provides a decision tree to determine whether a microorganism of concern is an objectionable microorganism when found in a nonsterile product.
Risk Based Decision Methodology

Objectionable Organism Decision Tree

Definitions

Growth in Product
1. Water Activity
2. Antimicrobial effectiveness test
3. Challenge

Organisms of Concern
1. Associated with outbreaks
2. Produced recalls
3. Clinically significant infections

Preservative Activity

Growth in product

Route of administration

Intended Population

High risk

Risk to Patient

Accept

Immune-compromised

Infant

Geriatric

High risk

Low risk

No

Accept

Objectable Organism

Accept

No

Objectable Organism

Objectable Organism

Low risk

No

Accept

No

Accept
Conclusions  consensus and findings from the benchmarking survey.

• The frequency of product recalls for objectionable microorganisms is low, and the incidence of infections traced back to the use of contaminated products is extremely low and primarily associated with the recipient’s health condition.

• Nevertheless, the nonsterile product manufacturers share customer and regulatory agency concerns about the serious health hazards that objectionable microorganisms can pose and wants to continuously improve manufacturing controls, detection and decision making to exclude objectionable microorganisms from its products.

• This report provides the framework for risk mitigation, and the authors offer the following recommendations:
  – A risk-based approach must be used for determining the level and type of testing to be conducted to identify potentially objectionable microorganisms in different products.
  – Standard microbiological testing procedures may be used with slight modifications to screen products for objectionable microorganisms.
Conclusions (Cont.)

• Organisms of concern must be identified based on a review of the published literature, such as the reference materials cited in this technical report.

• The technical report does not provide a list of objectionable microorganisms but does provide the framework for determining whether microorganisms in products are objectionable because the authors believe that only manufacturers have sufficient information about the ingredients, manufacturing processes, product attributes and intended use of their products to make informed decisions about whether a microorganism found in a specific product is objectionable in that product.

• Manufacturers of nonsterile products are encouraged to develop technically sound policies, procedures and training that ensure the exclusion of objectionable microorganisms from their products. These policies and procedures must result in consistent decision making that complies with the applicable regulations.
Inter-Associations Project on Drug Shortage
Deliverables

1. Harmonised definition of a meaningful disruption to supply
   - Notification from MAH to impacted competent authorities
     - National Medical Agencies assess:
     - The need for coordination between stakeholders
   - EMA assess for CAPs and where coordination between stakeholders are needed

2. Harmonised reporting template with initial categorisation based on PDAs triaging model
   - Agreed action plan between MAH and each impacted National Medical Agency

3. Harmonised time point and recipient of the information at NCA and EMA

Quality and Manufacturing Driven Supply Disruptions

Industry Communication Principles to Authorities

An Industry Collaborative Contribution to the EMA (European Medicines Agency) Initiative to Provide European Union Patients with Continuous Access to Medicines
Risk-Based Prevention of Drug Shortage

• Foundational concepts
  1. Risk-based triage of products
     • How to establish preventive end-to-end controls for drug shortage risks based on criticality of the product, patient impact and overall product risk evaluation.
  2. Establishment of a Product Risk Register and a product Drug Shortage Prevention and Response Plan
     • A holistic framework and simple templates at product level

• Where are we with our concept?
  – The concept including ready-to-use templates is fully completed after extensive discussions with the PDA membership and regulators
  – Feedback used actively in development of Technical Report. Aligned with EFPIA/EGA/AESGP/PPTA communication plan

• We are on track with our deliverables
  1. Triage approach communicated in the PDA Journal article April 2014
  2. Product Risk Register and Drug Shortage Prevention & Response Plan
     • Discussions at all signature PDA conferences since 2012;
     • Drug Shortage workshop Sept 2014; workshop proceedings – Dec 2014
     • Technical Report: Send draft for review – Oct 2014; target TR & training for the content 1Q 2015
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<tr>
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<td>May 2013</td>
<td>• R05: Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: Case Studies in the Packaging and Labeling of Drug Products</td>
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