The Pharmaceutical Supply Chain Initiative
Training for Auditors

Compiled by:
PSCI Audit Committee
Objective of the Training

1. PSCI /Processes
   - PSCI Principles and Implementation Guidance
   - Audit Guidance, Audit Report Templates and DSA

2. Understanding Unique Hazards in the Pharmaceutical Industry
   - Process Safety Management
   - Guidance for Identifying And Mitigating Dust Hazards
   - Inherently Safer Chemical Reactions
   - Pharmaceutical Ingredients in the Environment (PiE)
   - Managing Potent and Sensitizing Compounds
Objective

• This training session has been prepared for Pharmaceutical Supply Chain Initiative (PSCI) Auditors. It is intended to supplement their skills and provide insight into some unique hazard areas in the pharmaceutical industry and to assist the auditors with a baseline understanding of those hazards and some of the common concerns related to them.
The PSCI: who we are

The Pharmaceutical Supply Chain Initiative

An industry body formed by the pharmaceutical sector whose members share a vision for responsible supply chain management, to deliver better social, environmental and economic outcomes in the communities where they buy
The PSCI Principles: our guideposts

As a first step, the PSCI created the Pharmaceutical Industry Principles for Responsible Supply Chain Management ("the Principles")

These Principles address five areas of responsible business practices and the relevant standards any business operating within the pharmaceutical supply chain is expected to uphold.
The PSCI Principles Implementation Guidance

• The PSCI Principles articulate broad descriptions of what is expected.
• The Implementation Guidance Document illustrates some examples of how to meet those expectations.
Audit Guidance Document

- is available on the PSCI website
- provides the methodology on how PSCI audits are conducted and managed
- Gives a detailed overview of the audit process
- Clarifies auditor qualifications and roles/Responsibilities

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Right tools for the right audit
Audit tools: Audit Report Templates

- There are 2 audit report templates available
  - one for supply chain manufacturers (API/Finished dosage manufacturers..)
  - other for service providers and non-supply chain goods
- These Audit Report templates combine the SAQ with auditor verification and should be used for both the SAQ by the supplier and for verification of the auditor
Reminder: Use of data sharing agreement (DSA)
Unique Risks in the Pharmaceutical Industry

- PSM (process safety management) - Flammable Liquid/Gases/Dusts Handling Practices
- Guidance for Identifying & Mitigating Dust Hazards
- Inherently Safer Chemical Reactions
- PiE (Pharmaceuticals in Environment)
- Managing Potent and Sensitizing Compounds
Process Safety Management
Flammable Liquid/Gases/Dusts Handling Practices

• NFPA /ATEX Compliant
• Regulatory Compliance
• Closed Processing
• Closed Transfers
• Closed Sampling
• Highly Protect Risks Protection Design
  – Sprinklers
  – Suppression Systems
  – Explosion Relief Systems
Introduction

• Dust powders present a significant risk of fire and explosion hazards
• To minimize this risk, all facilities that handle solid materials must conduct a risk assessment for dust hazards to safeguard the health and safety of employees and protect the business
• This risk assessment should comply with OSHA Directive No. CPL 03-00-006, 18-Oct-2007 or ATEX requirements
• Results of risk assessment must be used to implement measures for mitigating these hazards
Guidance for Identifying & Mitigating Dust Hazards in Pharmaceutical Industry (2)

Risk Assessment Guidelines

- Document hazard properties of powders. If data is not available, additional testing should be done
- Classify areas into zones for electrical classification
- Determine risk & explosion severity for all equipment
- Where risk is identified, prepare action plan to mitigate risk
- Ensure safe working environment and appropriate surveillance when workers are present around equipment
Testing for Hazard Properties of Powders

• For initial screening, following tests are recommended:
  – Minimum Ignition Energy (MIE)
  – Minimum Ignition Temperature (MIT)
  – Thermal Stability
  – Explosion Severity (Kst)

• For powders having MIE of <25 mJ, following additional tests should be conducted:
  – Volume Resistively and Charge Relaxation Time

• Classification of Risks:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low Risk</th>
<th>Medium Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min. Ignition Energy (MIE)</td>
<td>&gt;100 mJ</td>
<td>25 to 100 mJ</td>
<td>&lt;25 mJ</td>
</tr>
<tr>
<td>Min. Ignition Temp. of Dust Cloud (MIT)</td>
<td>&gt;500 degC</td>
<td>300-500 degC</td>
<td>&lt;300 degC</td>
</tr>
<tr>
<td>Explosion Severity (Kst)</td>
<td>&lt;50 bars-m/sec</td>
<td>50-200 bars-m/sec</td>
<td>&gt;200 bars-m/sec</td>
</tr>
<tr>
<td>Thermal Stability</td>
<td>No exotherm</td>
<td>Exotherm &gt;200 degC</td>
<td>Exotherm &lt;200 degC</td>
</tr>
</tbody>
</table>
Guidance for Identifying & Mitigating Dust Hazards in Pharmaceutical Industry

Conditions for a Dust Explosion

- Material should be combustible (most organics are)
- Dust should be dispersed in air
- The dust concentration should be above the minimum explosive limit
- Enough oxidant (air) should be available
- Enough energy should be available for ignition (sparks, hot surfaces, flame from welding, electrostatic energy etc.)
- Dust must be in confined space

Dust Explosion Prevention by Proper Ventilation

- Maintain hood rates and velocities
- Keep ventilation systems balanced to prevent dust fall out and accumulation in ductwork
- Keep ducts clear of build up and deposits of materials
- Manage dust collection bag houses (dust collectors)
- Use ant-static bags and ground bag cages
- Inspect and maintain relief systems
Dust Explosion Protection Methods

Preventative measures alone may not ensure adequate levels of safety. Protective measures should be taken as well.

**Added Bases of Safety**

- Containment by explosion resistant construction
- Explosion venting to a safe place
- Explosion suppression by injecting a suppressant
- Inerting
- Explosion isolation

The embedded file below details layer of protection for various pharmaceutical processing equipment and should be reviewed by all auditors before completing a PSCI audit.

Classical dust collector with EX vent

Classical dust collector with suppression protection
Inherently Safer Chemical Reactions

Chemical Reaction Hazard Identification

- Know the heat of reaction for the intended and other potential chemical reactions.
- Calculate the maximum adiabatic temperature for the reaction mixture.
- Determine the stability of all individual components of the reaction mixture at the maximum adiabatic reaction temperature.
- Understand the stability of the reaction mixture at the maximum adiabatic reaction temperature.
- Determine the heat addition and heat removal capabilities of the pilot plant or production reactor.
- Identify potential reaction contaminants.
Inherently Safer Chemical Reactions (2)

Chemical Reaction Hazard Identification

• Consider the impact of possible deviations from intended reactant charges and operating conditions.

• Identify all heat sources connected to the reaction vessel and determine their maximum temperature.

• Determine the minimum temperature to which the reactor cooling sources could cool the reaction mixture.

• Consider the impact of higher temperature gradients in plant scale equipment compared to a laboratory or pilot plant reactor.

• Understand the rate of all chemical reactions.

• Consider possible vapor phase reactions.

• Understand the hazards of the products of both intended and unintended reactions.

• Consider doing a Chemical Interaction Matrix and/or a Chemistry Hazard Analysis.
Inherently Safer Chemical Reactions (3)

Reaction Process Design Considerations

- Reactor venting must be designed for worst credible case design.
- Rapid reactions are desirable.
- Avoid batch processes in which all of the potential chemical energy is present in the system at the start of the reaction step.
- Use gradual addition or “semi-batch” processes for exothermic reactions.
- Avoid using control of reaction mixture temperature as the only means for limiting the reaction rate.
- Account for the impact of vessel size on heat generation and heat removal capabilities of a reactor.
- Use multiple temperature sensors, in different locations in the reactor for rapid exothermic reactions.
- Avoid feeding a material to a reactor at a higher temperature than the boiling point of the reactor contents.
Concern with Pharmaceuticals in the Environment ("PiE")

- Pharmaceuticals in the Environment (PIE) has moved from an “emerging” issue to a “current high profile” public perception issue.
- Pharmaceutical compounds are being detected in streams, rivers and lakes.
- Concern that human health & aquatic life impacts may result from environmental exposure to these compounds.
- PIE directly impacts business reputation.
Patient Use is the Primary Pathway Human Pharmaceutical Compounds Enter the Environment
Pharmaceuticals in Environment

Human Health & Aquatic Species Impacts

• Human Health Impacts: APIs are being detected in drinking water, but at levels below any demonstrated impacts on human health.

• Aquatic Species Impacts: APIs, especially hormones, detected in surface water are being cited as cause of adverse effects in aquatic species, i.e., feminization of male fish.
PIE (Pharmaceuticals in Environment) “OBJECTIVE”

- Complete an Environmental Fate & Effects Assessment to determine if Active Pharmaceutical Ingredients (APIs) losses are impacting the environment:
  - Comply with FDA & EMEA New Drug Application requirements;
  - Determine acceptable levels of APIs in emissions & effluents from manufacturing sites necessary to protect the environment; see Link to recorded Webex: (39 minutes) https://pfizeruc.webex.com/pfizeruc/ldr.php?RCID=f22c8f2081b3ee3cae2a89c32bc9e017
  - Ensure good manufacturing practices are being followed to minimize the discharge of APIs to the waste water discharge, I. E. equipment cleaning, area wash down, etc.
  - Determine need & cost for “at source” or “end-of-pipe” treatment; and,
  - Control environmental impact relative to the API they are dealing with.
## PiE: Audit questions to be considered

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
<th>Comments</th>
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<tr>
<td>47. Has the facility developed and implemented a waste and wastewater management practices?</td>
<td></td>
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<tr>
<td>Do the practices cover:</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
<td></td>
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<td>Characterization of all wastes generated at the facility, including returned products, with regard to regulatory classification (e.g. hazardous waste, special waste, infectious waste, non-regulated solid waste, low-level radioactive waste) and hazardous properties (e.g. flammability, corrosiveness, toxicity)?</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are wastes that contain Active Pharmaceutical Ingredients (APIs) managed in such a way that the API is destroyed via that waste management method?</td>
<td>Yes</td>
<td>No</td>
<td></td>
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</tr>
<tr>
<td>Are there measures in place to ensure that API, drug product, and branded materials are not diverted from the intended waste treatment/disposal method/facility?</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the facility evaluate the discharge of wastewater to surface waters, onsite treatment works or offsite treatment to determine potential Active Pharmaceutical Ingredient (API) impact?</td>
<td>Yes</td>
<td>No</td>
<td></td>
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<tr>
<td>(considerations include: treatability, bioaccumulation potential, biotoxicity potential, and the capacity and capability of on-site treatment works, off-site treatment works, or Publicly Owned Treatment Works (POTWs) receiving the wastewater discharges to effectively perform treatment)</td>
<td></td>
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<tr>
<td>Are potential APIs in wastewater subject to treatment, capture, and containment practices to reduce API levels to no effect levels when practical?</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td>Comments:</td>
</tr>
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Managing Potent and Sensitizing Compounds
What sites should have

- An onsite person who has had training in control of hazardous agents
- Access to expert (e.g. certified industrial hygienist, qualified consultant)
- Inventory of hazardous chemical agents, in particular potent (OHC 4 and 5) materials, sensitizers, carcinogens and reproductive hazards.
- Information on chemical agents from customers and suppliers and use of a banding system
- Access to MSDS data and communication of risks, procedures and controls to staff using the hazardous agents.
- Chemical risk assessments – chemicals used, operations performed, assessment of control measures (including non-production tasks such as maintenance of equipment, handling of waste)
- Procedures and training on storage / use and cleaning of PPE.
- Sampling and monitoring data as appropriate
- Risk based health surveillance.
- Incident/exposure records
Examples: Process Equipment – Charge, Blend & Mill

- Uncontrolled

- Controlled
Managing Potent and Sensitizing Compounds
Pharmaceutical Hazard Banding

Compounds assigned to OHC banding based on:

- Potency
- Pharmacological effects
- Toxicological effects of API
- Different schemes for different pharmaceutical companies
Managing Potent and Sensitizing Compounds

Exposure Control Banding

• Example of exposure control banding:
  – OEB 1 (>1000 ug/m3)
  – OEB 2 (100-1000 ug/m3)
  – OEB 3 (10-100 ug/m3)
  – OEB 4 (1-10 ug/m3)
  – OEB 5 (<1 ug/m3)
Managing Potent and Sensitizing Compounds
Factors Influencing Exposure

- **Less Containment**
  - Scale: Gram
  - Dustiness: Coated tablets, Tablets, Wet Cake, Granules, Powders, Micronized
  - Process Energy: Weighing/Dispensing, Charging/discharging, Milling/sieving
  - API content: 1%, 10%, 100%

- **Increased Containment**
  - Behaviours: Good behaviours, Poor behaviours

The image shows a comparison of containment levels and behaviours across different scales and processes.
Managing Potent and Sensitizing Compounds

Further Information

- PSCI
  - http://pharmaceuticalsupplychain.org/
- International Occupational Hygiene Association
  - http://www.ioha.net/index.html
- OH Learning.com
  - http://www.ohlearning.com/
For more information…

visit: www.pscinitiative.org

Or

Email us: info@pscinitiative.org

Thank you for your time and attention!