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PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

The Pharmaceutical Supply Chain Initiative Training for Auditors

Compiled by:
PSCI Audit Committee

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Agenda

1. Objective of the Training
2. PSCI /Processes
   - PSCI Principles and Implementation Guidance
   - Audit Guidance, Audit Report Templates and DSA
3. 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

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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 to 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.

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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

Currently 17 member companies

abbvie
ALLERGAN
AstraZeneca
Baxter
BAYER
biogen idec
Boehringer Ingelheim
Bristol-Myers Squibb
gsk GlaxoSmithKline
Johnson & Johnson
Lilly
Mallinckrodt Pharmaceuticals
MERCK
NOVARTIS
Pfizer
Roche
West

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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

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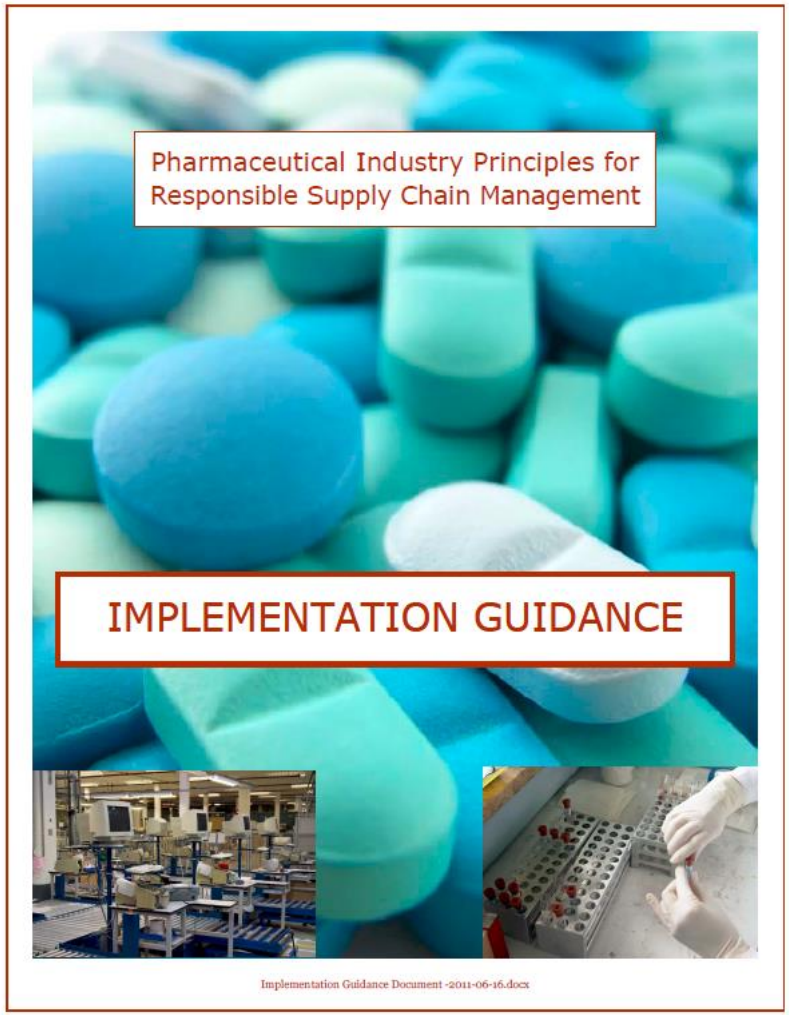
The PSCI Principles Implementation Guidance

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



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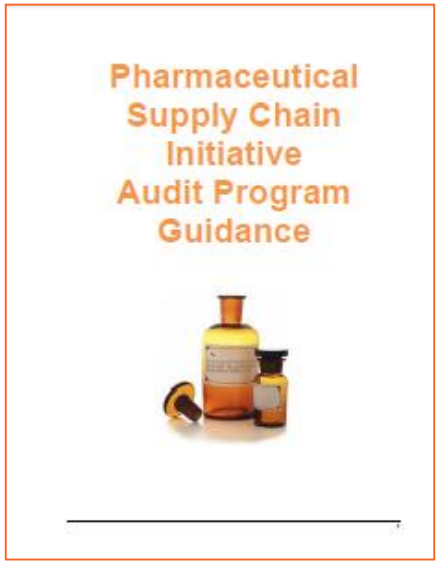
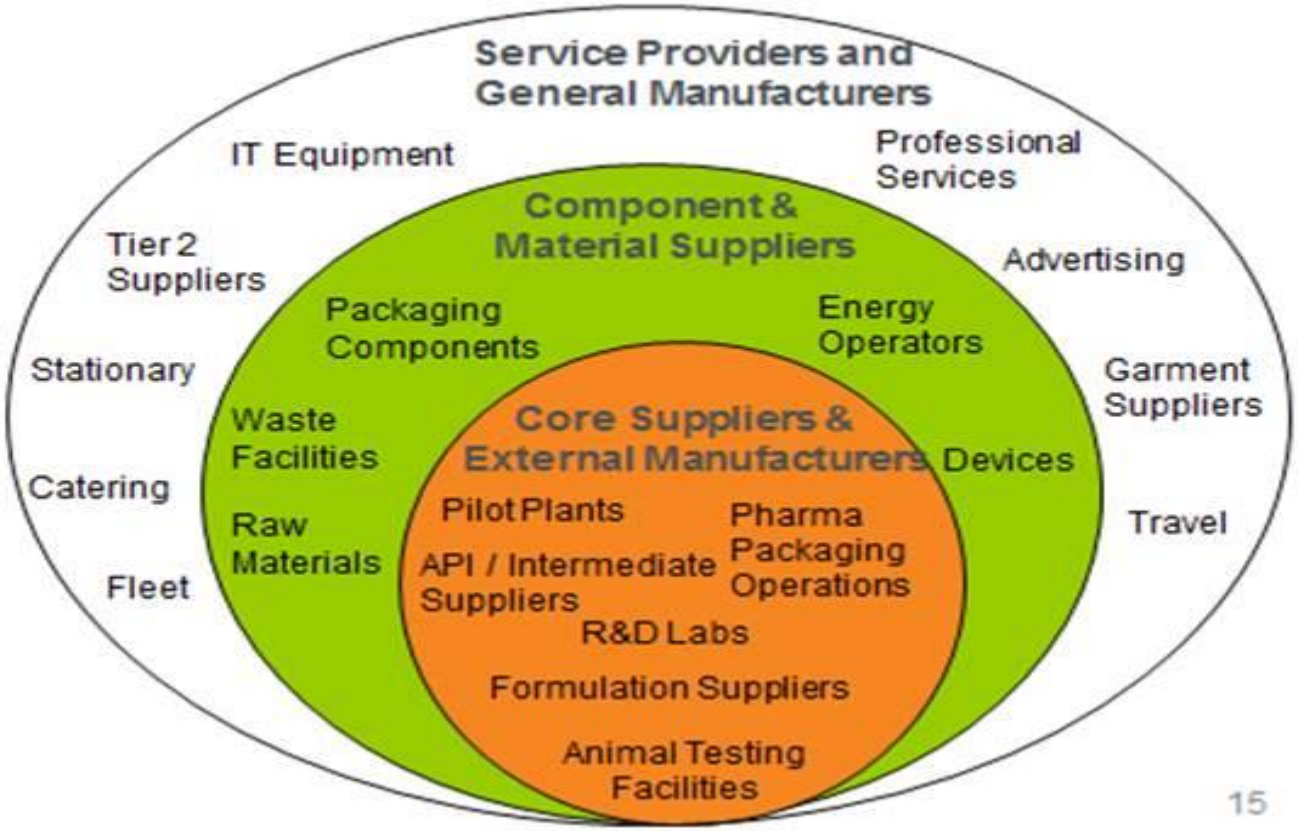
Audit Guidance Document

- 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



Contents

Right tools for the right audit



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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

MANAGEMENT SYSTEMS			Auditor Verification
Commitment and Accountability			
1	Does the facility have any ethics, labor, environment, health and safety management system accreditations, certifications, or awards?	OHSAS 18001 Yes ☐ No☐ ISO 14001 Yes ☐ No☐ SA8000 Yes ☐ No☐ Other (e.g. Awards, OSHA VPP, EMAS):	Yes ☐ No ☐ Comments
2	Does management engage employees in open two-way communication?	Yes ☐No☐ Please explain:	Yes ☐ No ☐ Comments
Legal and Customer Requirements			
3	What is the current situation related to Ethics, Labor, Environment, Health, and Safety (EHS) Regulatory Compliance?	Is there any ongoing litigation or regulatory notices with respect to regulatory compliance? Yes ☐ No☐ Are there any historical major regulatory actions? Yes ☐ No☐ Any continuous / prolonged situations where regulatory compliance requirements are exceeded? Yes ☐ No☐ Please explain:	Yes ☐ No ☐ Comments
4	Does the facility assess ongoing compliance with Health, Safety, and Environment, and labor regulations?	Yes ☐ No☐ Please explain:	Yes ☐ No ☐ Comments
5	Has the company endorsed the PSCI Principles?	Yes ☐No☐	Yes ☐ No ☐ Comments
6	Does your facility ensure that your suppliers operate good practices with regards to the PSCI Principles (i.e., labor, ethics, environment, health & safety, and management systems)?	Yes ☐ No☐ If yes, please explain how:	Yes ☐ No ☐ Comments

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Reminder: Use of data sharing agreement (DSA)

Return completed form to PSCI@bsr.org

Pharmaceutical Supply Chain Initiative
(PSCI) DATA SHARING AGREEMENT

The Pharmaceutical Supply Chain Initiative (PSCI) is a group of major pharmaceutical companies who share a vision of better social, economic and environmental outcomes for all those involved in the pharmaceutical supply chain. This vision is detailed in the PSCI Principles and includes improved conditions for workers, economic development and a cleaner environment for local communities.

The members of PSCI recognize the burden that is created for your company by multiple information requests and onsite audits of your sustainability performance. In order to reduce this burden, PSCI has created standardized protocols and tools for assessing suppliers' alignment with the PSCI Principles.

We are currently employing these tools with a group of select suppliers and would like to invite your company to participate.

Specifically, we ask you to complete a Self-Assessment Questionnaire (SAQ), and agree to an on-site audit. Both the SAQ and on-site audit process have been designed to minimize time requirements, while still ensuring that we capture the detailed information that is required.

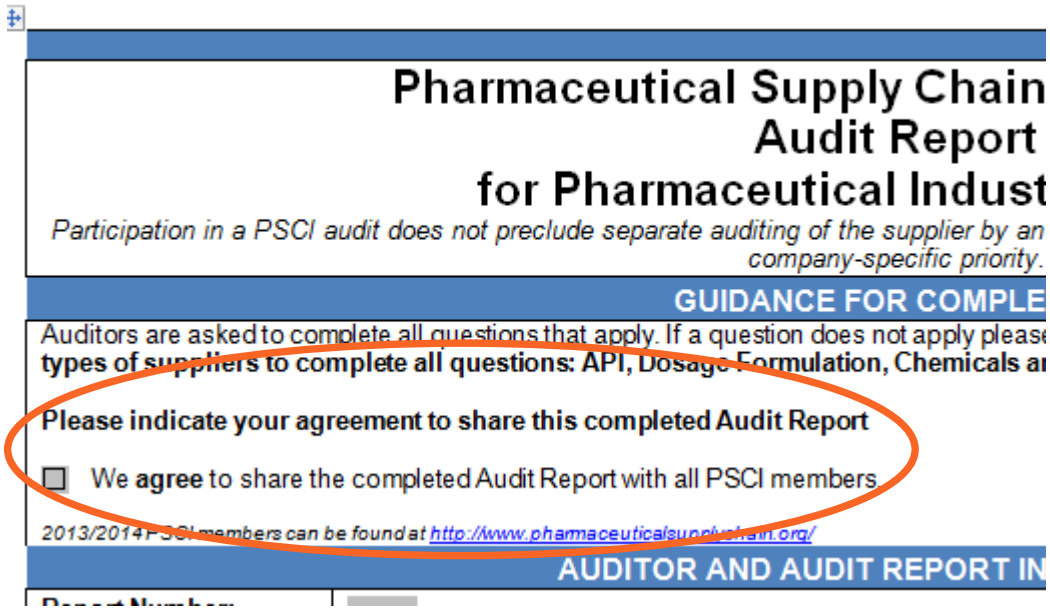
PSCI agrees to maintain the confidentiality of all SAQs, audit reports, corrective action plan reports, supplier correspondence, and other supplier facility records, and to use such information only for the purpose of evaluating or monitoring the suppliers' facilities in accordance with the PSCI Principles.

In order to reduce the burden of multiple requests for information, you hereby authorize PSCI to share the audit reports and related information with the PSCI members, including any new member that joins PSCI in the future. The list of PSCI members, as updated from time to time, can be found online at: http://www.pharmaceuticalsupplychain.org.

Process for participating suppliers:

- Complete data sharing agreement (this document) and PSCI Self-Assessment Questionnaire, returning both documents—within two weeks—to PSCI Secretary at PSCI@bsr.org.
- PSCI will inform you, the supplier, of path forward for audit.
- When audit proceeds, PSCI-selected auditor will contact supplier directly to arrange next steps; PSCI will have provided the auditor with your completed SAQ in advance of the audit.
- Supplier data will be shared with PSCI members. Supplier may choose to share data with additional persons.
- Individual PSCI members may follow-up directly with supplier.

Supplier Details	*PSCI Details*
Company name: _____	Pharmaceutical Supply Chain Initiative
Address: _____	Address: _____
Name/Title of person completing this form:	Name/Title of person completing this form:
_____	_____
Contact details (email and phone):	Contact details (email and phone):
_____	_____
Signature: _____	**Signature:** _____
Date: _____	**Date:** _____



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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

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

Guidance for Identifying & Mitigating Dust Hazards in Pharmaceutical Industry (1)

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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)

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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:

Parameter	Low Risk	Medium Risk	High Risk
Min. Ignition Energy (MIE)	>100 mJ	25 to 100 mJ	<25 mJ
Min. Ignition Temp. of Dust Cloud (MIT)	>500 degC	300-500 degC	<300 degC
Explosion Severity (Kst)	<50 bars-m/sec	50-200 bars-m/sec	>200 bars-m/sec
Thermal Stability	No exotherm	Exotherm >200 degC	Exotherm <200 degC

Guidance for Identifying & Mitigating Dust Hazards in Pharmaceutical Industry

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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

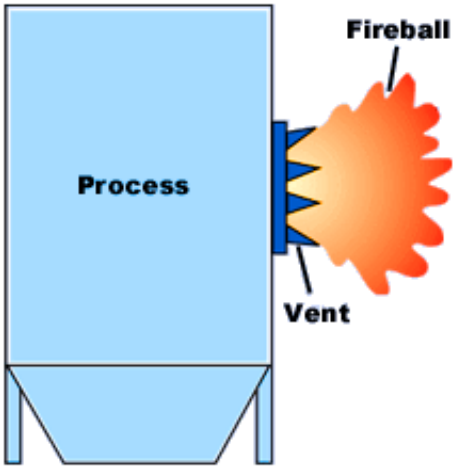
Preventative measures alone may not ensure adequate levels of safety. Protective measures should be taken as well.

Added Bases of Safety

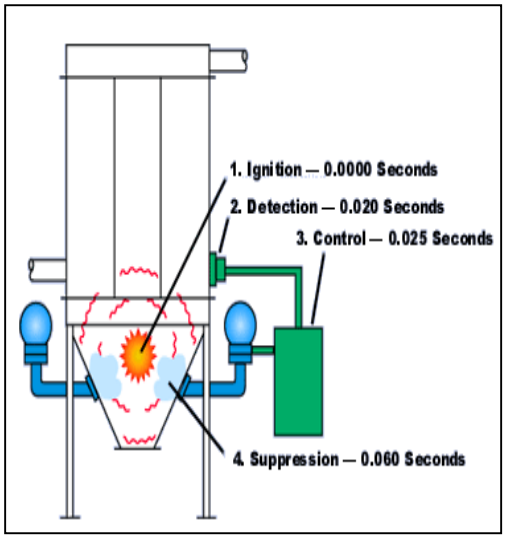
- Containment by explosion resistant construction
- Explosion venting to a safe place
- Explosion suppression by injecting a suppressant
- Inerting
- Explosion isolation

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.

Adobe Acrobat Document



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.

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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”)

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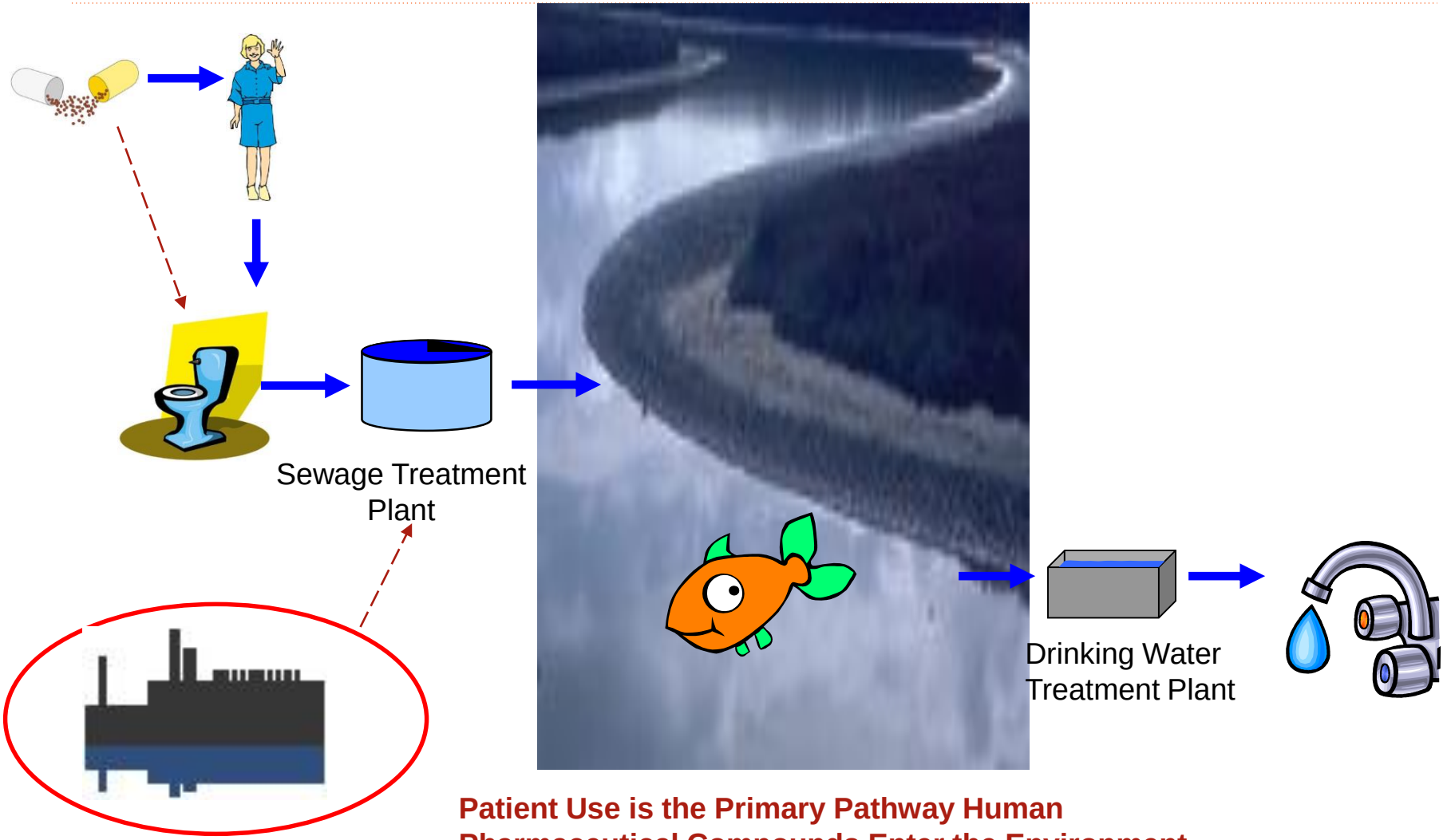
- Pharmaceuticals in the Environment (PIE) has moved from an “emerging” issue to a “current high profile” public perception issue.
- Pharmaceutical compounds are being detected in streams, rivers and lakes.
- Concern that human health & aquatic life impacts may result from environmental exposure to these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

Pharmaceuticals in the Environment



Patient Use is the Primary Pathway Human Pharmaceutical Compounds Enter the Environment

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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"

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- 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.

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PiE: Audit questions to be considered

47	Has the facility developed and implemented a waste and wastewater management practices?	Yes ☐ No ☐ N/A ☐ Do the practices cover: 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)? Yes ☐ No☐ Are wastes that contain Active Pharmaceutical Ingredients (APIs) managed in such a way that the API is destroyed via that waste management method? Yes ☐ No☐ 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? Yes ☐ No☐ 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? Yes ☐ No☐ *(considerations include: treatability, bioaccumulation potential, bio-toxicity 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)* Are potential APIs in wastewater subject to treatment, capture, and containment practices to reduce API levels to no effect levels when practical? Yes ☐ No☐ Comments:	Yes ☐ No ☐ Comments

Managing Potent and Sensitizing Compounds
What sites should have

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- 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

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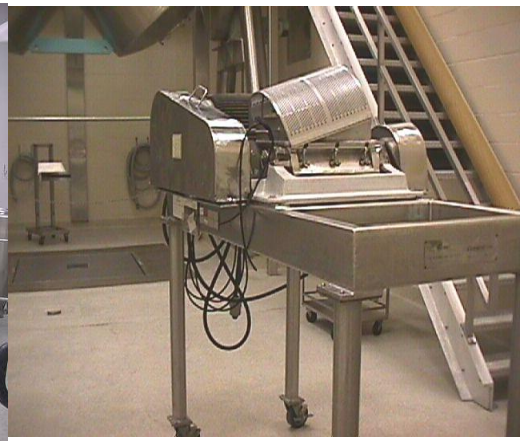
- Uncontrolled





- Controlled


Managing Potent and Sensitizing Compounds Pharmaceutical Hazard Banding

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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

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- 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

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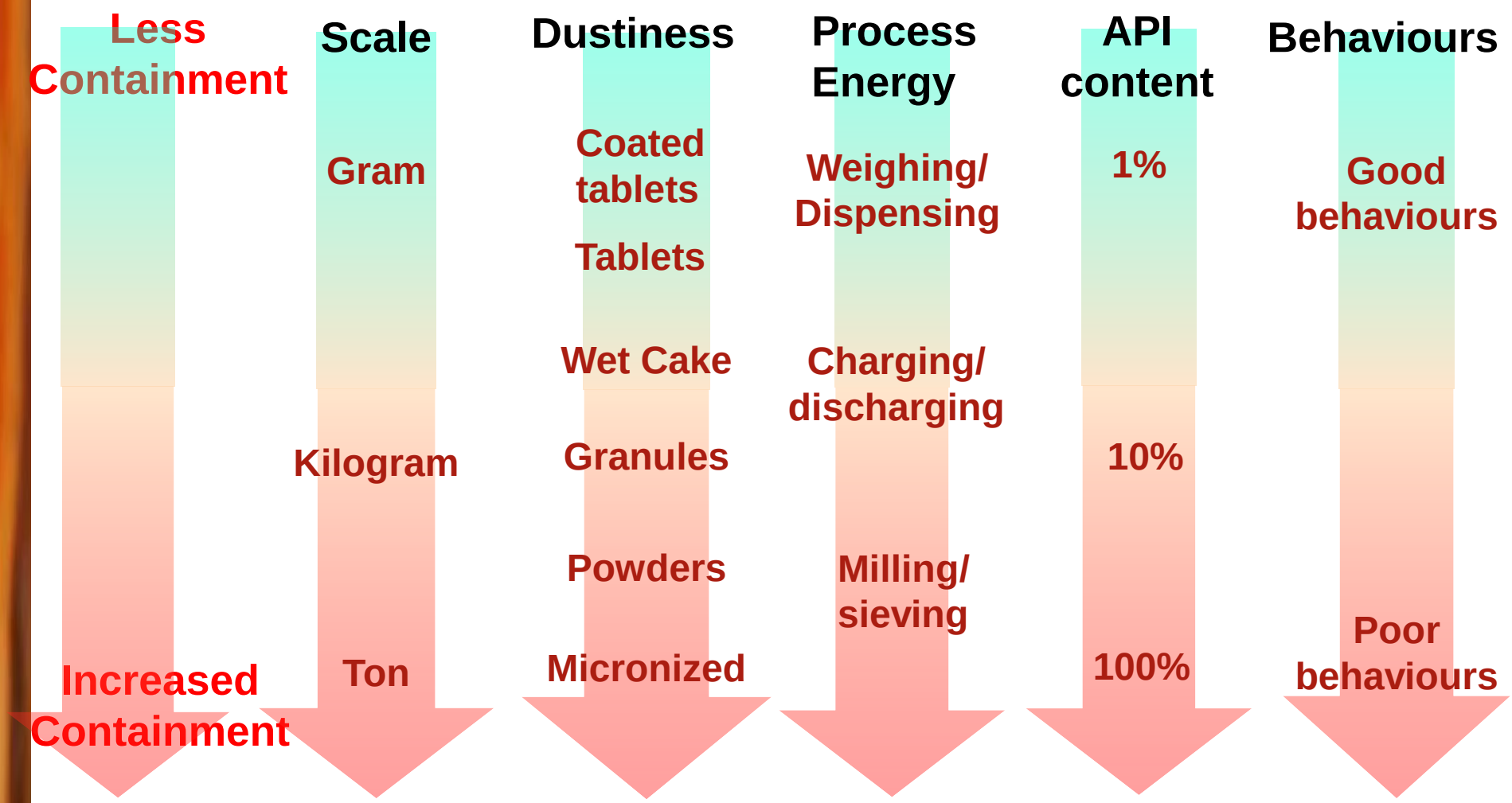

Managing Potent and Sensitizing Compounds Further Information

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

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For more information…

visit: www.pscinitiative.org

Or

Email us: info@pscinitiative.org

Thank you for your time and attention!