PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

PSCI Auditor Training 2018
Day 1

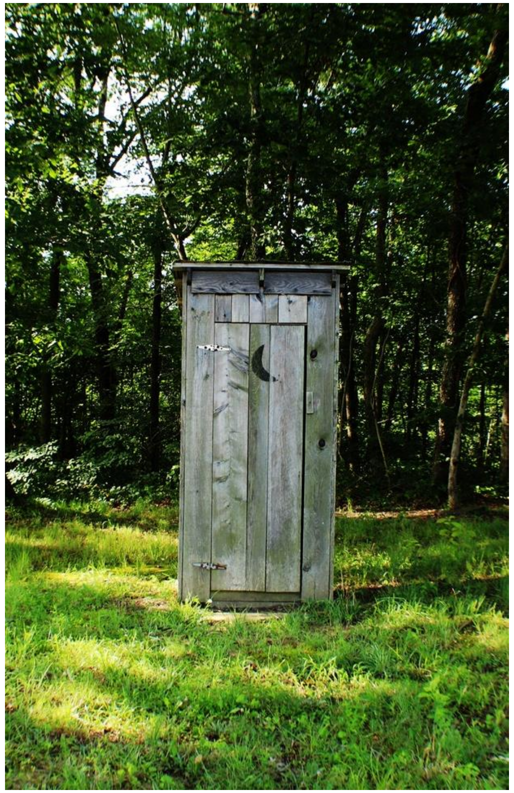
Vienna, 4 – 5 December 2018

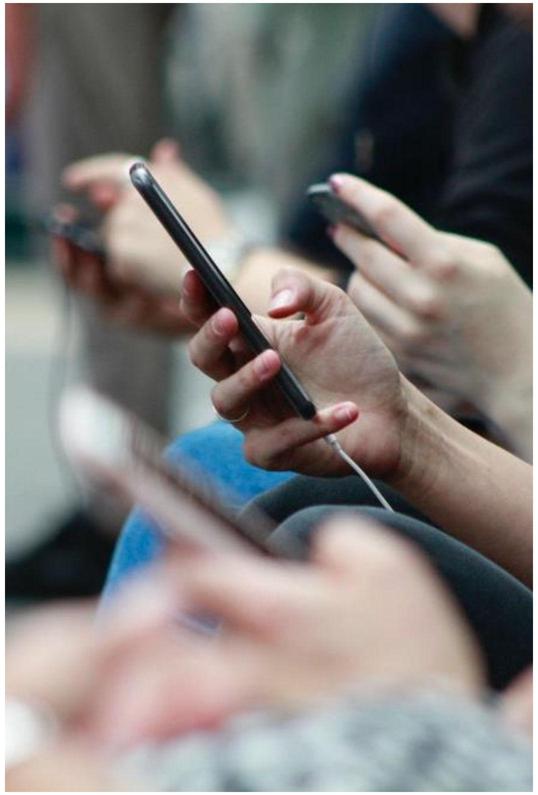
Markus Katzler

- 5 years in German nuclear power plants - inspections of safety equipment
- Immuno/Baxter/Baxalta/Shire
  - Electrical Engineering in the field of Energy monitoring and Systems
  - EHS Environmental Management, Energy and EHS Audits
  - Head of EHS for the last 7 years
- Engineer in Electronic and Telecommunication
- New father

Shire is the leading global biotechnology company focused on rare diseases

HOUSEKEEPING





INTRODUCTIONS

Doreen Parrish
Shire

Dr Birgit Mertens
J&J

Benoit Baruteau
Sanofi

Dr Stefan Gries
Boehringer Ingelheim

Tristan Edmondson Carnstone

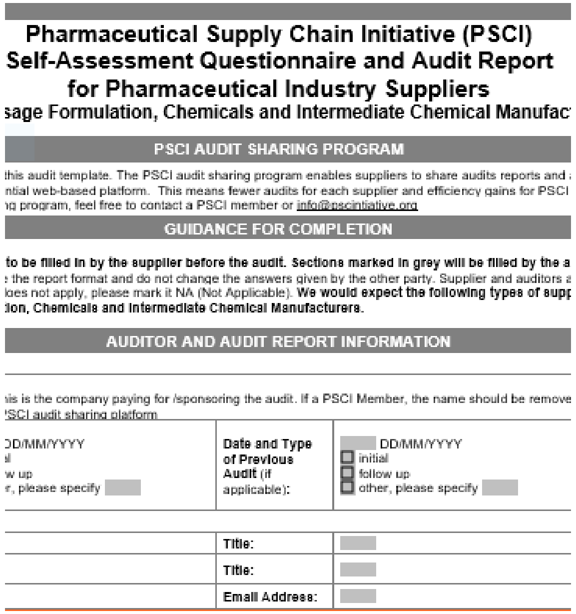
William Pickett
Carnstone

INTRODUCTIONS

1. Name
2. Company
3. Years auditing
4. Number of pharma audits
5. One thing you want from today

WHY ARE WE HERE?

To ensure that all auditors meet the minimum qualifications and experience required to conduct PSCI audits, and to improve the overall quality of the PSCI shared audits.


Pharmaceutical Supply Chain Initiative (PSCI)
Self-Assessment Questionnaire and Audit Report
for Pharmaceutical Industry Suppliers
sage Formulation, Chemicals and Intermediate Chemical Manufac

PSCI AUDIT SHARING PROGRAM

this audit template. The PSCI audit sharing program enables suppliers to share audits reports and
ntial web-based platform. This means fewer audits for each supplier and efficiency gains for PSCI
ng program, feel free to contact a PSCI member or info@pscintiative.org

GUIDANCE FOR COMPLETION

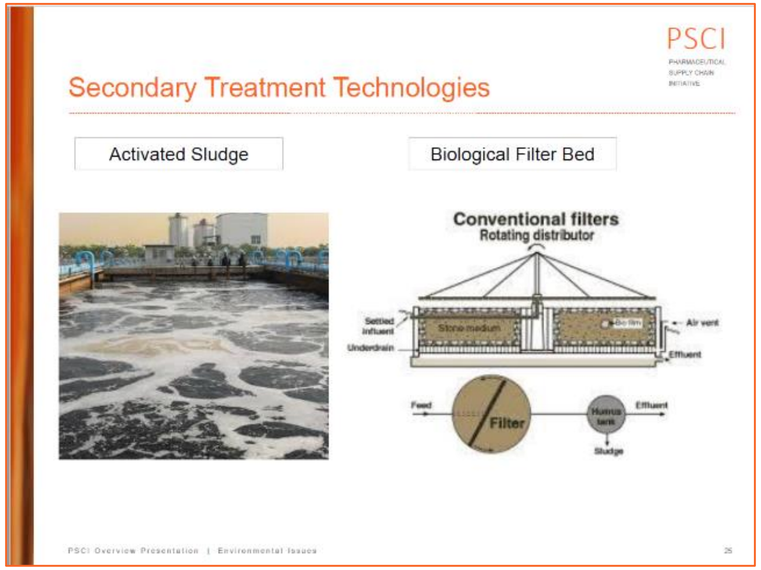
to be filled in by the supplier before the audit. Sections marked in grey will be filled by the a
the report format and do not change the answers given by the other party. Supplier and auditors a
does not apply, please mark it NA (Not Applicable). We would expect the following types of supp
tion, Chemicals and Intermediate Chemical Manufacturers.

AUDITOR AND AUDIT REPORT INFORMATION

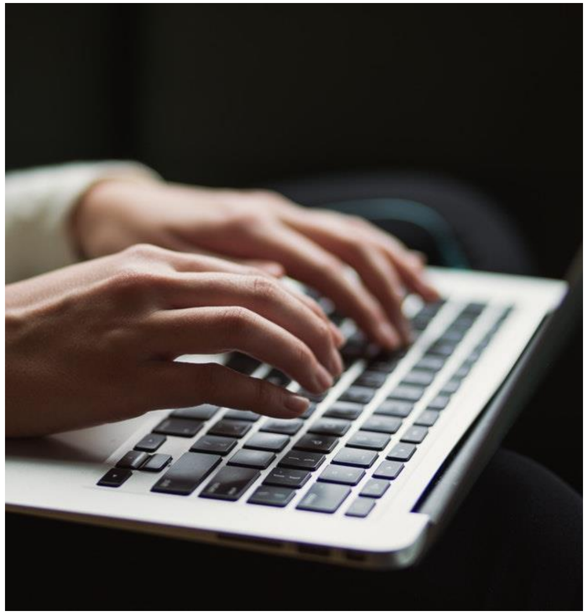
is is the company paying for /sponsoring the audit. If a PSCI Member, the name should be remove
PSCI audit sharing platform

DD/MM/YYYY l w up r, please specify	Date and Type of Previous Audit (if applicable):	DD/MM/YYYY initial follow up other, please specify
	Title:	
	Title:	
	Email Address:	

SAQ



Pharma Topics



Audit findings

DAY 1 AGENDA

Time	Activity	Speaker
08:30 – 09:15	Welcome, **Introduction to PSCI Audits** (45m)	Doreen Parrish/ Tristan Edmondson
09:15– 10:45	**General safety (**1h30)	Doreen Parrish
10:45 – 11:00	BREAK	
11:00 – 12:30	**Process safety 1** (1h30)	Dr Stefan Gries
12:30 – 13:30	LUNCH	
13:30 – 14:30	**Process safety 2** (1h)	Dr Stefan Gries
14:30 – 15:30	**Environmental protection 1** (1h)	Birgit Mertens
15:30 – 15:45	**Break**	
15:45 – 17:00	**Environmental protection 2** (1h15)	Birgit Mertens
17:00 – 17:30	EXAM Part 1	

DAY 2 AGENDA

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

Time	Activity	Speaker
08:00 – 08:30	Registration, coffee/tea	
08:30 – 10:30	**Occupational Health and Industrial Hygiene** (2h)	Doreen/ Benoit
10:30 – 10:45	BREAK	
10:45 – 12:30	**Emergency Preparedness and Response** (1h45)	Benoit Baruteau
12:30 – 13:30	LUNCH	
13:30 – 15:00	**High Risk work and red flags for dangerous working** (2h)	Doreen Parrish
15:15 – 15:45	EXAM Part 2	
15:45 – 16:00	Training wrap up	Tristan Edmondson

PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Building responsible supply chains

PSCI Auditor Training 2018
General Safety

Doreen Parrish, CPEA, CHMM

Head of EHS Systems & Continuous Improvement

Global Environment, Health & Safety - Shire

TRAINING STRUCTURE

1. Training / Competency
2. Incident Management
3. Machine Safety
4. Hazard Signage
5. Personal Protective Equipment
6. Circulation inside / outside of building

Training / Competency

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Building responsible supply chains

«There is no formal evidence that H&S training to employees is provided»

«The company has not provided HSE training to their employees confirmed through management interview»

«Workers are not formally trained for emergency preparedness and response and for health & safety topics.»

Some findings from the shared reports...

« The more you sweat in times of peace,
the less you bleed in times of war »
A former Navy Seal about training

Training Program

- What to look for ?
  - SOP, concept (Word or Powerpoint file)...
- When / how
  - During dedicated section
  - During review of high risk activities
- What good looks like
  - Topics mentioned in SAQ should be found in the training concept (see list on the right)
  - Strategy to capture new hires in the program

Ethics, Labor
Emergency preparedness/response
New employee orientation (HSE)
Annual HSE refresher training
Pre-start up process HSE training
Hazard Communication
Process Safety Management
Health Practices
Environmental Practices

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Building responsible supply chains

Training for activities with higher risks

- What to look for ?
  - Training regarding Risk Assessment and activities with higher risks like Working at Heights, Confined Space Entry, Working with Hazardous Energies...
- When / how
  - When reviewing a program dealing with higher risks, f.ex. PHA (Process Hazard Analysis).
  - Check the training records of the team that perform the analysis
- What good looks like
  - Formal training took place
  - Enough opportunities to practice and get/keep proficiency

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Training Matrix

- What to look for ?
  - Description which roles get which trainings
- When / how
  - When reviewing the topic
- What good looks like
  - At role or individual level
  - Usually 0.5% of working time (10h for full FTE)
  - External audience (contractors) is captured

Matrix - Role Base Training

		Site Mgmt		Site HSE Team				Lab / Pilot Plant			
Course Title/SOP Name	Global function heads	Site Head	Site leadership team	HSEO	HSE Co-ordinator	BC Coordinator	Energy manager	Pilot Plant Head	Pilot Plant Operator	Lab Head	Lab Worker
HSE & BC - General Overview											
Site Induction Course - general											
HSE Policy Site/Novartis											
HSE & BC Mgmt System Manual											
Incident/accident and near miss reporting											
Nov. Manu Manual											
CHSE Guidelines											
CHSE Guidance Notes											
Division Standards / Practice											
HSE by Design											
HSE and BC Management Systems											
Policy and Responsibilities											
Process Descriptions											
Risk Management											
Objective Setting, realisation and review											
Communication Processes											
Training , Awareness, Competencies											
Emergency Management - NEM Processes Overview											
Emergency Management - NEM Team members											
Incident investigation											
Non confromance and Corrective Action											
HSE performance management - monitoring and measurement											
Local HSE Regulatory requirements											
International relevant regulatory requirements											
Audit/inspections/management tours											
Hazard Specific Topics - where relevant											
Exposure to hazardous materials / Industrial Hygiene											

HSE Role based Training

Training Records

- What to look for ?
  - Attendance list, IT-system proof of attendance...
- When / how
  - When reviewing the topic
- What good looks like
  - Associate are identified by name or number
  - Associate have signed the sheet
  - IT-system is qualified for this task

Training attendance signature sheet

Process Hazard Analysis Awareness Training
Trainer : Frieda Nocera
November 12th 2018, 9am to 11am

Name	Employee number	Signature
Macy Weidler	49594	[illegible]
Zoe Golder	3332	[illegible]
Karisa Darnell	548712	[illegible]
Rheba Rother	862889	[illegible]
Elliott Spears	634947	[illegible]
Danyel Whitting	423820	[illegible]
Lynwood Bentler	331040	[illegible]
Terese Massaro	384728	[illegible]
Dustin Mistretta	902743	[illegible]
Joannie Mcnabb	587970	[illegible]
Roxie Milsap	388331	[illegible]
Quentin Guttman	944197	[illegible]
Noble Word	613786	[illegible]
Melodee Street	78903	[illegible]
Samantha Jankowski	84569	[illegible]
Latonya Coache	607144	[illegible]
Mandi Swan	428211	[illegible]
Ehtel Lovingood	589535	[illegible]
Keren Eyer	466949	[illegible]

Incident Management

«Accident reporting of contractors is not mandatory as required by PSCI»

«Fire extinguisher is obstructed by the table in the kitchen during tour»

Some findings from the shared reports...

« Putting the immediate causes right will prevent only the last accident happening again; attending to the underlying causes may prevent many similar accidents. » *Trevor Kletz*

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Reporting of accidents

- What to look for ?
  - Any kind of records ; could be paper based (cards, reports...) or through an IT-system
- When / how
  - During specific section or if an accident is mentioned then use this opportunity
- What good looks like
  - Check the number of reported events
  - Check the content's quality of a small sample

I was impressed when a voice on the office PA system announced, "This is a test of the PA system to ensure it will function correctly in case of emergency." My confidence faded when the voice added, "If you are unable to hear this announcement, please contact us."

How many ? (for a 500 FTE site)
TRCR of 1.0 = 5 cases per year
Near-Miss : 1 for 2 employees
250 per year = 20 per month

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Near Miss

- What to look for ?
  - Same as for accidents : paper records or IT-system
- When / how
  - If NM is identified during site tour, use the opportunity
- What good looks like
  - Number (could indicate a good reporting culture), quality of content
  - Who exploits the NM reports? are they tracked individually? any consolidation? any action plan derived from consolidated NM?

Root-cause Analysis

- What to look for ?
  - Reports (root-cause analysis itself)
  - Trend analysis – systematic weaknesses ?
- When / how
  - During review of the topic
- What good looks like
  - Fitness of the used methodology
  - Adequate training of the team members
  - Root cause identified (no «human error»)

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Action Plan and Follow-up

- What to look for ?
  - Action Plan itself
    paper, electronic document, IT-system
  - Any system to follow-up on actions
- When / how
  - During Incident Management or Risk assessment
  - Closure of actions can be checked during site tour
- What good looks like
  - Has to be effective : should be closed on time or escalated
  - Sufficiently large sample should be considered
  - System to make sure that individual Action Plans are not lost

Action Steps/ Tasks What will be done?	Responsibility Who will do it?	Timeline When will it begin and when will it be completed?	Resources What additional resources do you need?
Reserve two classrooms	**Michelé Robinson**	**Begin: 3/13 Completed: 3/13**	Rooms on campus
Schedule faculty for 'office hours' simulation	**Monica Edwards**	**Begin: 4/13 Completed: 5/13**	None
Schedule Library research visit	**Monica Edwards**	**Begin: 4/13 Completed: 5/13**	None
Schedule Financial Aid presentation	**Kris Hoffhines**	**Begin: 4/13 Completed: 6/13**	Financial aid representative commitment
Notify Success Services of student visits over a 2 week period	**Michelé Robinson**	**Begin: 4/13 Completed: 6/13**	None
Notify Career Center of student visits over a 2 week period	**Michelé Robinson**	**Begin: 4/13 Completed: 6/13**	None
Develop college readiness pre & post assessment	**Monica Edwards & Laura LaBauve**	**Begin: 5/13 Completed: 6/13**	Assessment tool

Machine Safety

«The worker protection for cone type rotary dryers was not effective. When it keeps rotating, operators can open the barrier door and approach it. [...] all the cone type rotary dryers were not equipped with interlocl safety system for door barriers [...]»

«During facility tour it was noted that the machine does not have security device in danger zone»

«The site operates a number of old machinery without a conformity declaration or CE labelling»

Some findings from the shared reports...

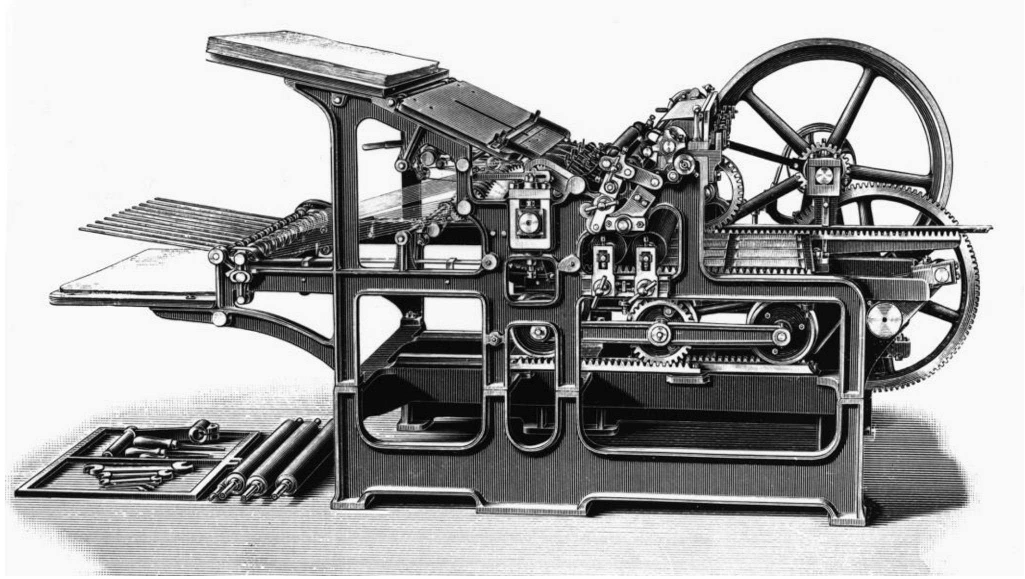
CE Certification

- What to look for ?
  - CE certification (documentation or tag on the machine (if available))
- When / how
  - During site tour, pick one machine (address other topics as well like risk assessment, preventive maintenance...)
- What good looks like
  - Legal compliance has to be ensured but focus on high risks

CE

Risk Analysis for old equipment

- What to look for ?
  - «old» machines should have been risked assessed and report should be available
- When / how
  - During site tour or after reviewing a new machine, ask «what about old ones?»
- What good looks like
  - Quality of risk assessment
  - Mitigation of identified risks implemented



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Modification of equipment

- What to look for ?
  - Obviously modified equipment
  - Machines / equipment trains
- When / how
  - Site tour
  - During review of documents related to risk assessment
- What good looks like
  - Quality of risk assessment

Hazard Signage

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«The site has not displayed fire exit evacuation route map across the plant.»

«Site has not displayed chemical compatibility chart at warehouse»

Some findings from the shared reports...

Hazard Signage

"One earnest worker can do more by personal suggestion to prevent accidents than a carload of safety signs." E.R. Brown

Uniformity

- What to look for ?
  - Any strategy for hazard signage, SOP
  - Example in the production / utilities area
- When / how
  - Ask question during site tour if issues are seen
- What good looks like
  - Same look and feel

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Quality

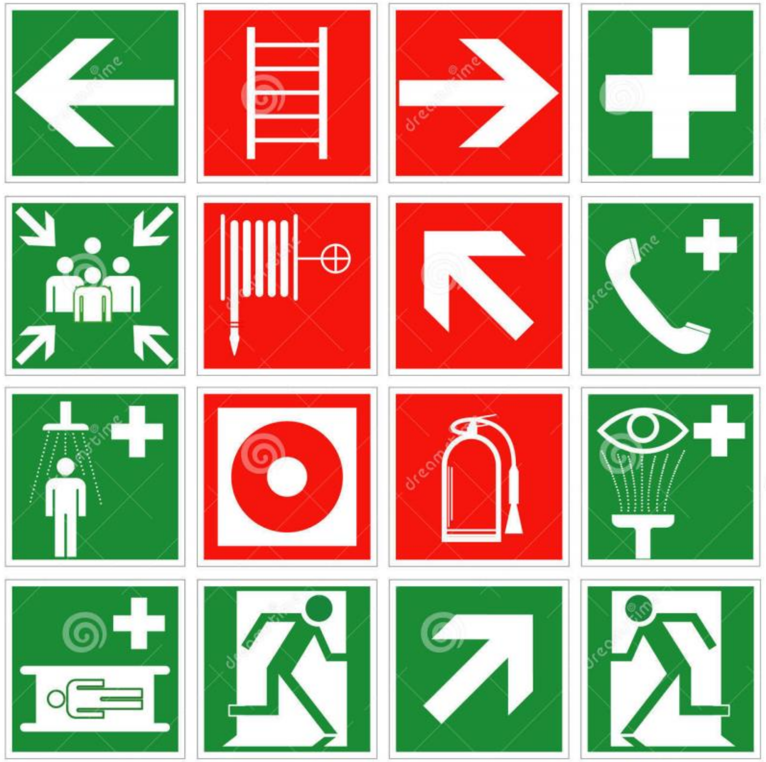
- What to look for ?
  - Signs in different languages, old, poorly visible
- When / how
  - Ask question during site tour if issues are seen
- What good looks like
  - If associates are speaking different languages, pictures might be better compared to text
  - Signage needs to be visible and of good quality
  - New machines might have signage in the language of the manufacturer, not local one !

Quantity

- What to look for ?
  - Situation during site tour with an excess of hazard signs
- When / how
  - Ask question during site tour if issues are seen
- What good looks like
  - Let to the judgement of the auditor based on experience

Emergency signage

- What to look for ?
  - Situation where emergency signage is not appropriate
- When / how
  - During site tour
- What good looks like
  - Compliance with local / national legislation
  - Judgement of the auditor based on experience



Personal Protective Equipment

«Assignment of PPE in the production area is not clear to audit team.»

«Label points out gasmasks and other PPE are mandatory but they are only worn when it is necessary. Also safety glasses were not permanently worn in the production area.»

Some findings from the shared reports...

According to STOP principle, Personal Protective measures should be the last barrier but it is often used as the first and only one.

Adequacy of proposed PPE

- What to look for ?
  - Risk assessment defining PPE needs
  - Maintenance of some type of PPE
- When / how
  - During risk assessment review
  - During site tour, when seeing particular PPE in use
- What good looks like
  - PPE are defined based on risk assessment
  - Associate are not overprotected
  - Use of PPE is done correctly

Circulation in/outside buildings

«One C[...] owned truck at a loading bay was observed not to be secured by safety wedges while being loaded by a fork lift truck as required by German Regulation [...]»

«It was observed that material was stored all around in the packaging room. There was no reflective strip pasted on the floors to maintain the walkway width»

Some findings from the shared reports...

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Segregation between walkers and traffic

- What to look for ?
  - Crowded areas with a lot of goods movements (not only in warehouses)
- When / how
  - During site tour
- What good looks like
  - Dedicated pathway
  - Markings on the grounds
  - Traffic lights...

Forklift operations

- What to look for ?
  - Goods movements inside and outside of building
- When / how
  - Concept, SOP can be reviewed during desktop assessment
  - During site tour, good opportunity to observe behaviors
- What good looks like
  - Legal requirements vary but drivers should normally be officially trained

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Chemical Process Safety: Which parameters are important to perform a chemical reaction in a safe way?

Dr. Stefan Gries
Boehringer Ingelheim Corporate Center, Corp. EHS&S

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Dr. Stefan Gries

- Chemist
- More than 25 years with Boehringer Ingelheim
- Current position: Corp. EHS & S (occupational health, exposure control, soil and groundwater protection, EHS auditor)
- Former positions in
  - Local EHS (Safety Engineer)
  - Research & Development (Head of pilot plant)
  - Chemical Production (Head of production plant)

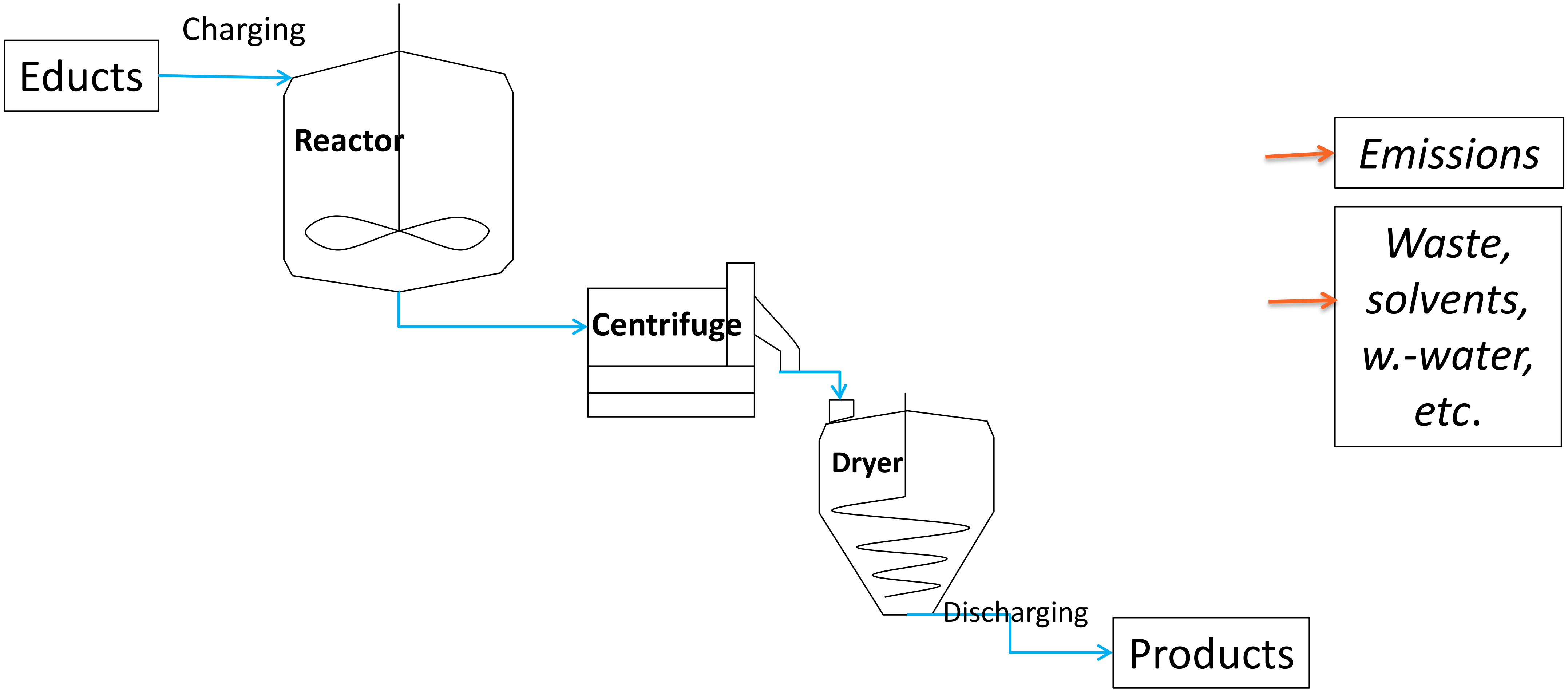
TRAINING STRUCTURE

1. Session 1
- Process safety parameters
- Essential information to chemical processes
- Critical interactions of material
- Exothermic and run-away reaction
- Scale up

2. Session 2
- Runaway reaction
- PSCI Questionnaire & Typical Observations

3. Audience questions & discussions

Chemical reaction in a production plant



Which information is necessary for a safe process?

- Knowledge about the used chemicals regarding thermal stability, physical safety parameters and toxicology
  - Educts
  - Products (incl. side products)
  - Reagents
  - Solvents & Auxiliaries

- Knowledge about the chemistry
  - Main reaction and side reactions
  - Waste streams (gas release, liquids and solids)
  - Consecutive reaction, decomposition?

- Reaction type
  - Batch reaction
  - Semi-batch reaction
  - Continuous flow reaction

What is necessary for a safe process?

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- Calorimetric data of the chemical reaction
  - Adiabatic temperature rise
  - Gas evolution rate (→ reactor venting sufficiant?)
  - precipitation of solids (→ reduction of heat transfer, stirrer blocking?)
  - Accumulation of reactants, thermal output/time
  - Stability of reaction mixtures, distillation residues, etc.
  - Potential for runaway reaction, abnormal operating conditions
  - If necessary: investigation of the runaway reaction

- Knowledge about critical interaction between the used chemicals and other material
  - Material resistance of reactor & other equipment
  - Possible material contact (e.g. media supply)

What is necessary for a safe process?

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- Plant equipment “state of the art”
  - Materials of the equipment = > material tests, corrosive data, etc.
  - Inertisation of equipment
  - Earthing of the equipment, explosion-proof equipment
  - Blow-down system, pressure relief valve, rupture disc,
  - Heating and cooling medium & capacity
  - Safety concept e. g. for electrical shut down

→ Process Hazard Analysis

Examination of the chemical properties and chemical process safety data together with the technical installation of the plant.

A safe chemical process is always an adequate combination of safe substance handling, known chemical process and adapted equipment.

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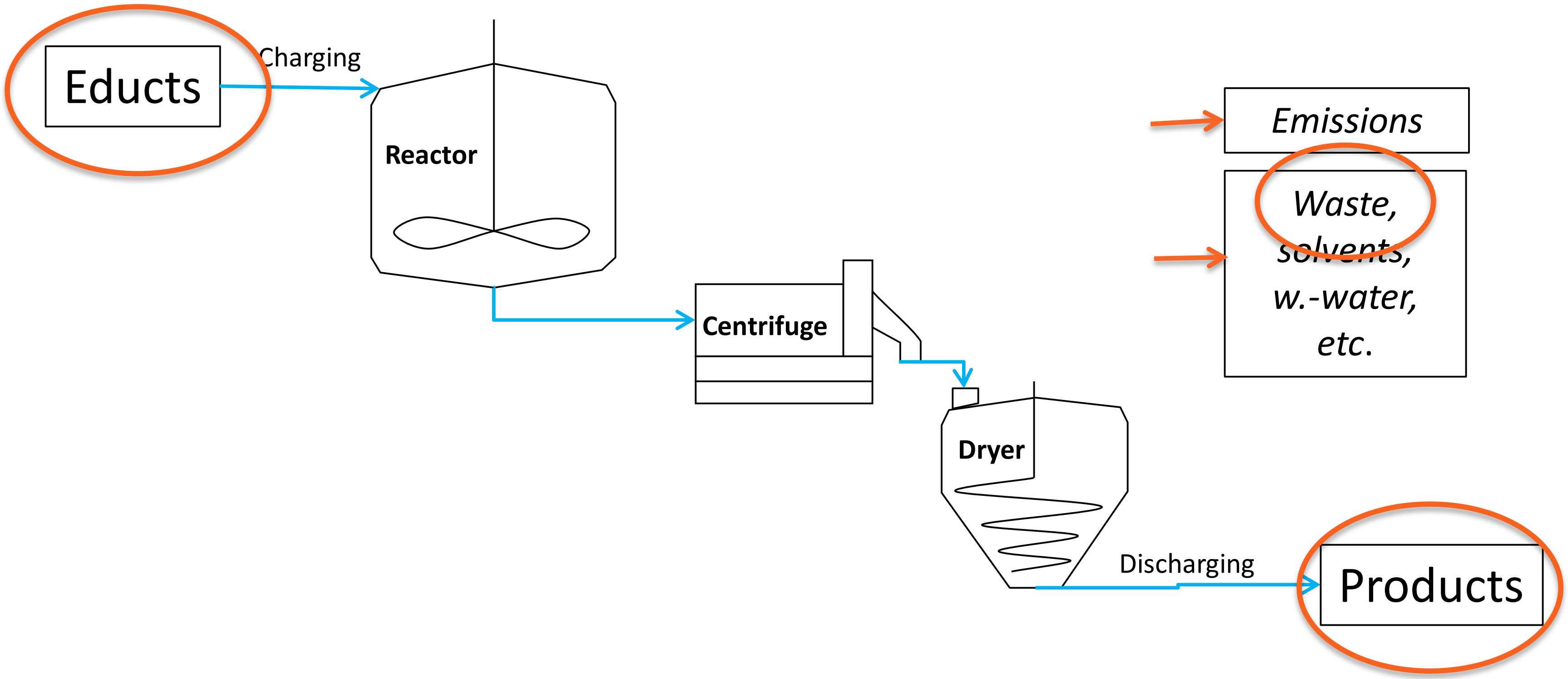
Thermal stability of chemical substances and reaction mixtures



Thermal stability of chemical substances and reaction mixtures

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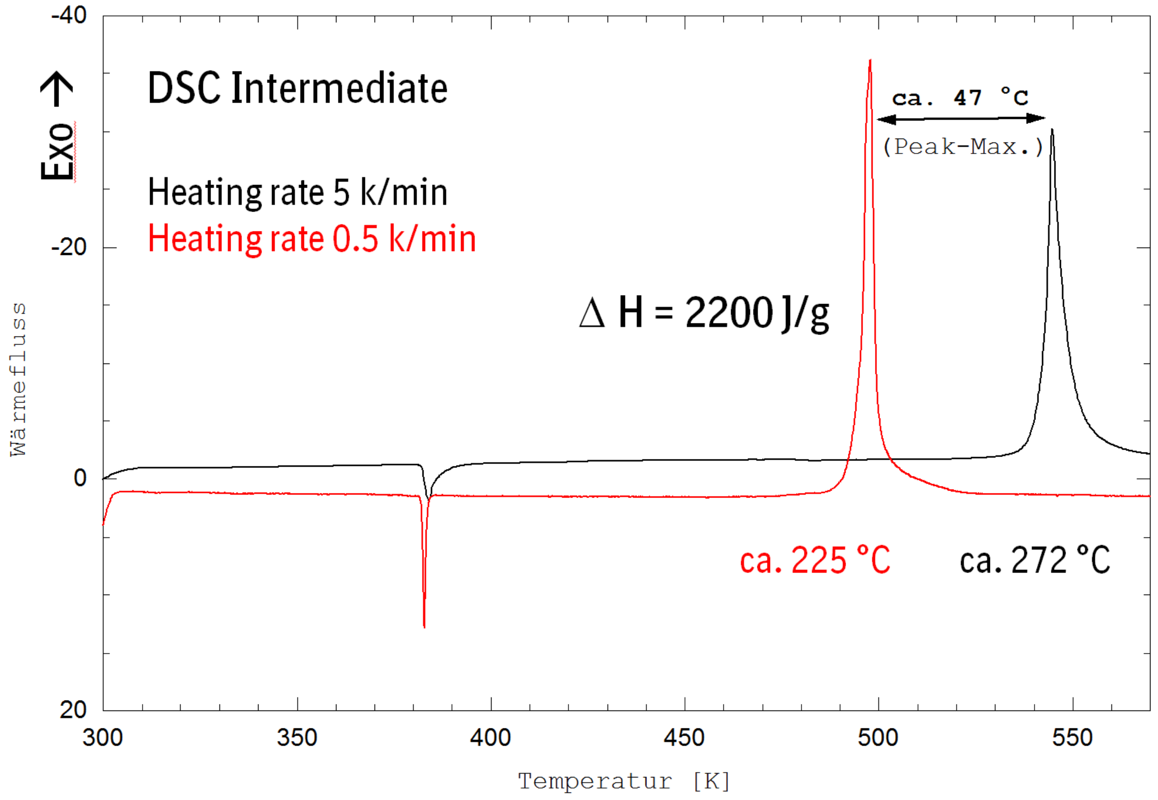
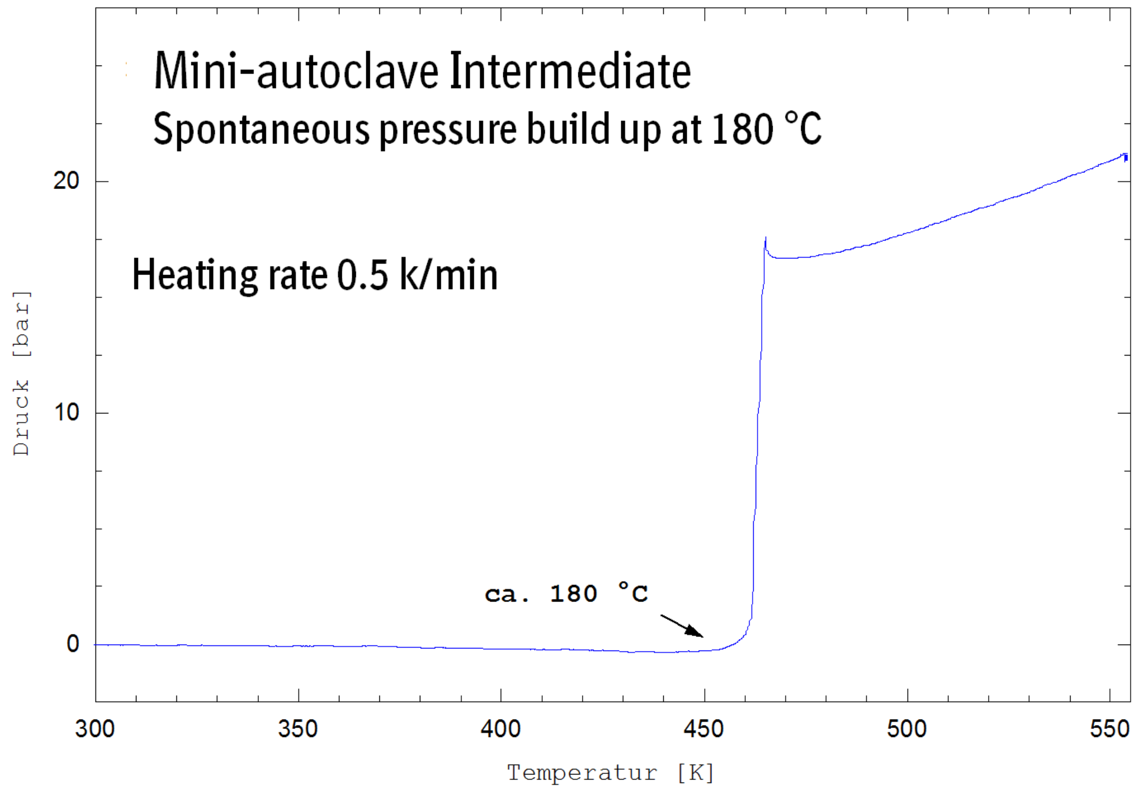
- Thermal stability:
  - Differential Scanning Calorimetry (DSC) or Differential Thermo Analyses (DTA)
- Decomposition test closed vessel (pressure build-up):
  - e.g. in a mini-autoclave





Known hazardous substances

- Typical chemical functions in thermodynamically unstable compounds:

-CΞC-	acetylene and acetylide
$-N_3$	azide and hydrogen azide
$-NΞN^+$	diazonium salts, triazene, tetrazene
-N=N-	azo compounds
-HN-NH-	hydrazide
>C=N=O	fulminates, oximates
>N-X	halogene nitrogene compounds
$-NO_x$	nitrites, nitrates, nitro- and nitroso compounds
-O-O-	peroxides, peroxy acids, ozonids
$-O-ClO_x$	(per-)chlorate, (hypo-)chlorite

Known highly reactive substances

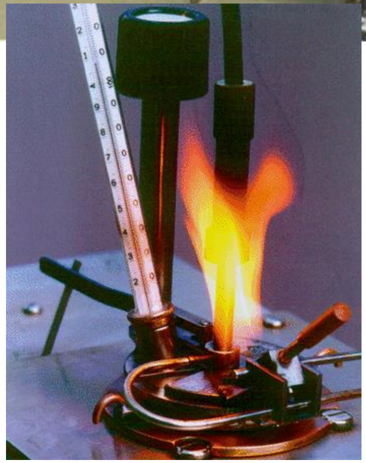
- Typical compounds or chemical functions:

R-Mg-X	Grignard reagents
R-Li	organic lithium compounds
-COCl	acid cloride
-CO-O-OC-	acid anhydride
Na-, K-OR	Sodium-, Potassium alkoholate
$POCl_3$, $SOCL_2$	inorganic anhydride
„H_2SO_4“	conc. acids, lyes
NaH, $LiAlH_4$	hydride
Na, K, Mg, Li …	metals
O_2, H_2	gases
F_2, Cl_2, Br_2	halogen

General handling characteristic of substances

- Additional test for thermal stability
  - Thermogravimetry (TG) or combination TG/DSC; TG/DTA
  - Quasi-adiabatic heat aging in a Dewar flask (or an adiabatic calorimeter)
  - Time Pressure Test

- Flammability of solids or liquids
  - Combustion test
  - Flammability of solids
  - Smoldering temperature; minimum ignition temperature of a dust layer
  - (minimum) dust cloud ignition temperature
  - Ignition temperature of liquids
  - Flash point (of liquids)



General handling characteristic of substances

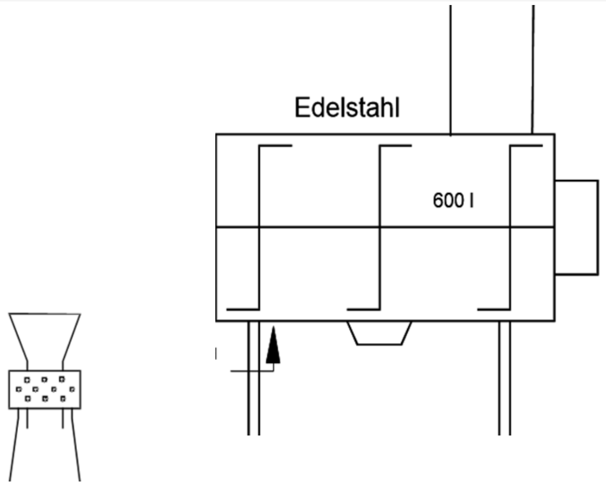
- Dust explosibility:
  - Dust explosion test
  - Dust explosion characteristics (p_{max}; $(dp/dt)_{max}$; K_{St}; explosion limits
  - Minimum ignition energy (MIE)

- Mechanical sensitivity, further safety characteristics
  - Sensitivity to impact
  - Sensitivity to friction
  - Self-ignition test
  - Conductivity

Details to: Dust stability/explosibility

- Mechanical sensitivity: Sensitivity to impact / friction

➢ Important for mechanical actions
(e.g. transport systems, in dryer with agitator, in a pin mill,)
→ maximum temperature & agitation time



- Maximum explosions pressure p_{max}

For most of the organic gases and vapors in mixture with air p_{max} is between 8 bar to 10 bar under initial atmospheric conditions.

➢ Important for e.g. venting pipes/filter units, for mills, dryers („dust containing air“)
→ explosion-resistant design

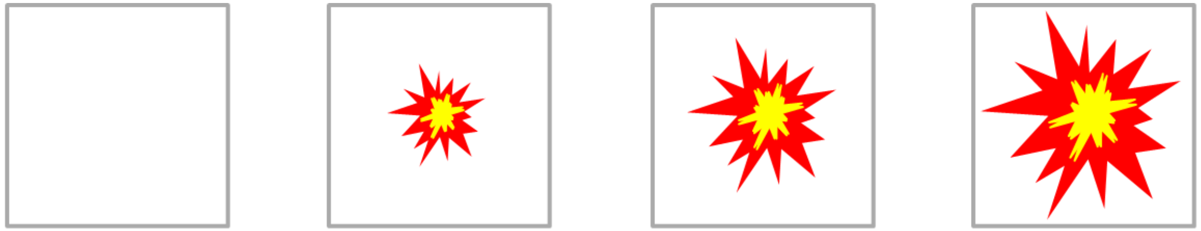
Details to: Flammability of solids or liquids

- Ignition temperature

Auto-ignition temperature (according to EN 14 522)	Temperature class	Maximum surface temperature
> 450 °C	T 1	450 °C
> 300 °C to 450 °C	T 2	300 °C
> 200 °C to 300 °C	T 3	200 °C
> 135 °C to 200 °C	T 4	135 °C
> 100 °C to 135 °C	T 5	100 °C
> 85 °C to 100 °C	T 6	85 °C

Details to: Dust explosibility

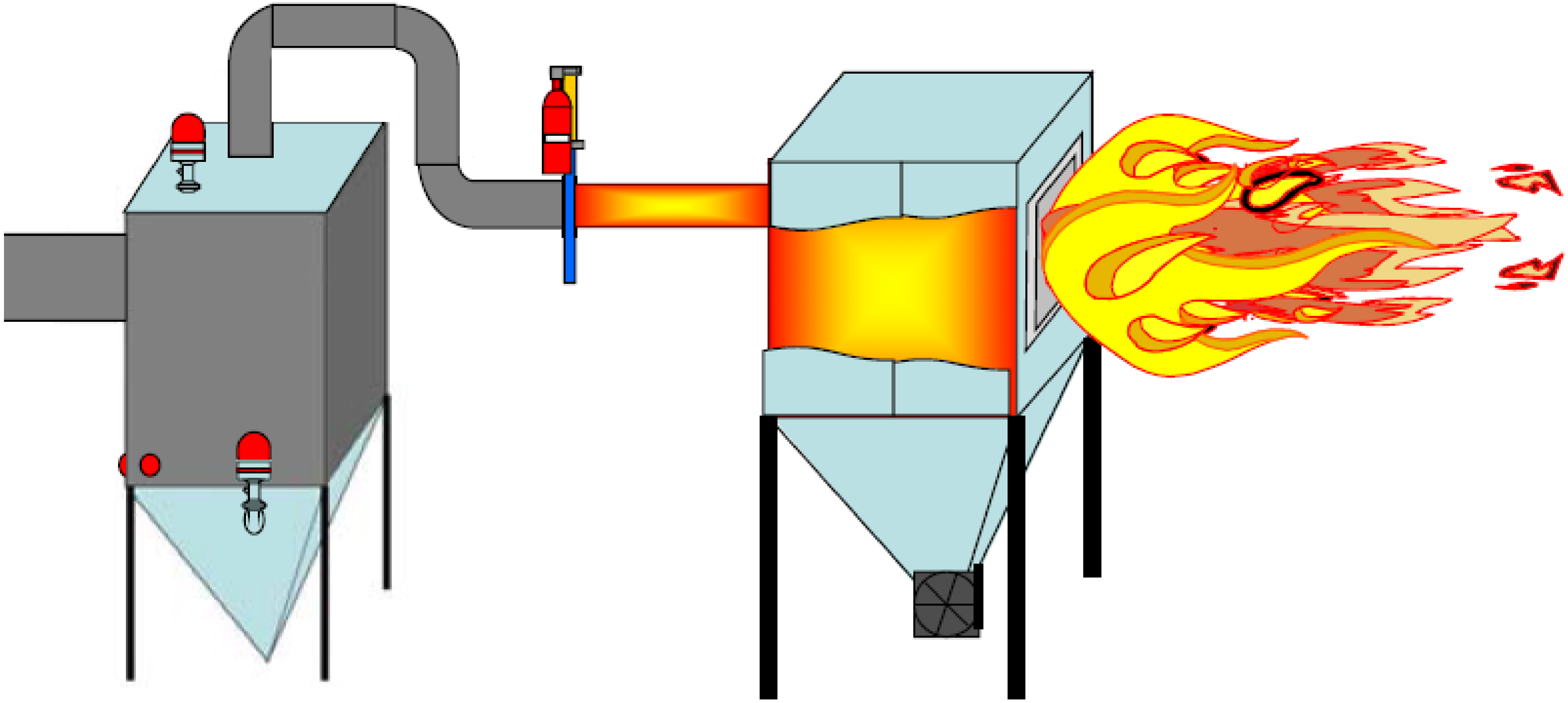
- Maximum explosion pressure rise $(dp/dt)_{max}$ and K_{St}



Dust explosion group	St 0	St 1	St 2	St 3
Kst bar.m.s^{-1}	0	$> 0 \leq 200$	$> 200 \leq 300$	> 300
Explosion characteristics	no explosion	weak/ moderate	strong	very strong

➢ Important for design of “explosion relief“, “explosion suppression” system

Examples of Process Equipment

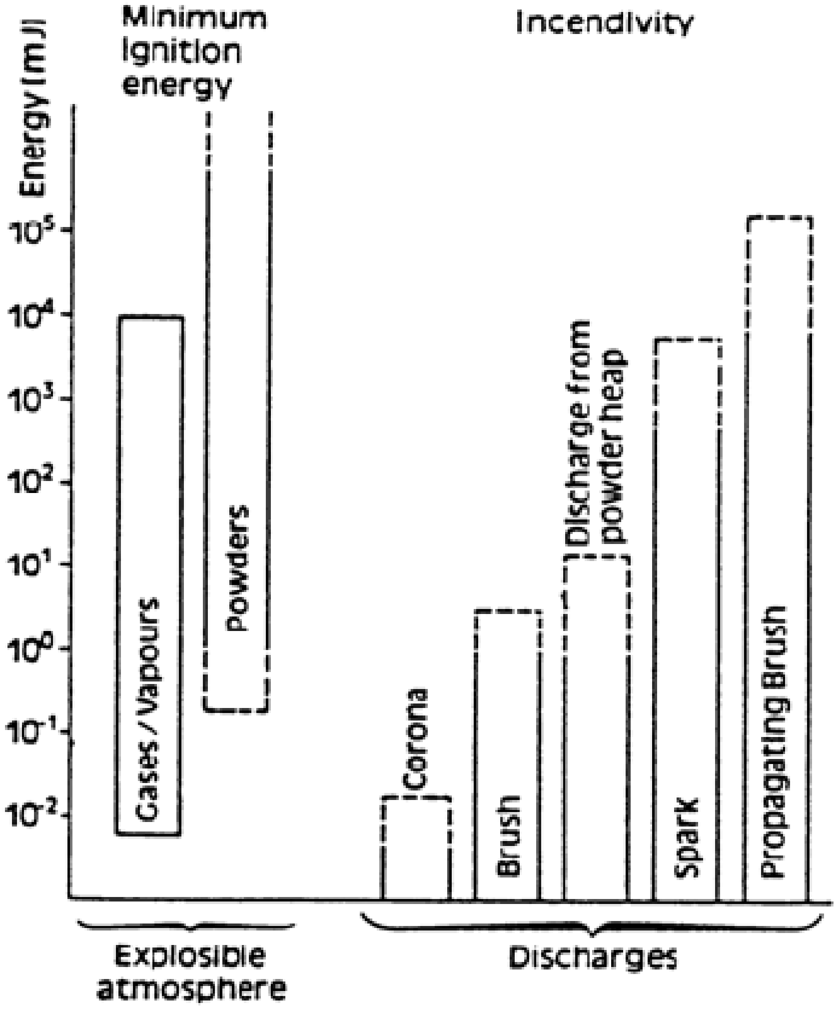


- If the K_{st} is above 300 bar m/s, the valve would not work

Details to: Dust explosibility

- Minimum ignition energy (MIE)

Risk	Substance Name	MIE in air
High risk < 25 mJ	Hydrogen	0.01mJ
	Methanol	0.14 mJ
	n-HeptanE	0.24 mJ
	Acetone	1.15 mJ
	“Normal organic" dust	>10 mJ
	Paracetamol	<10 mJ
Medium risk 25 – 100 mJ	Wheat flour	~50 mJ
	Sugar powder	30-100 mJ
	Coal	30-100 mJ
Low risk >100 mJ	PVC	1500 mJ



Resulting technical requirements of equipment

	Temperatur Class					
Explosion Group	T1 (> 450° C)	T2 (> 300° C)	T3 (> 200° C)	T4 (> 145° C)	T5 (> 100° C)	T6 (> 85° C)
IIA	Acetone Acetic acid Methane Propane Ammonia Benzene Toluene	Fuel Methanol Butan	Hexane Diesel Fuel oil	Acetal-dehyde		
IIB	Hydrogen cyanide	Ethanol Ethane	Hydrogen sulfide			
IIC	Hydrogen					Carbon disulfide

What is necessary for a safe process?

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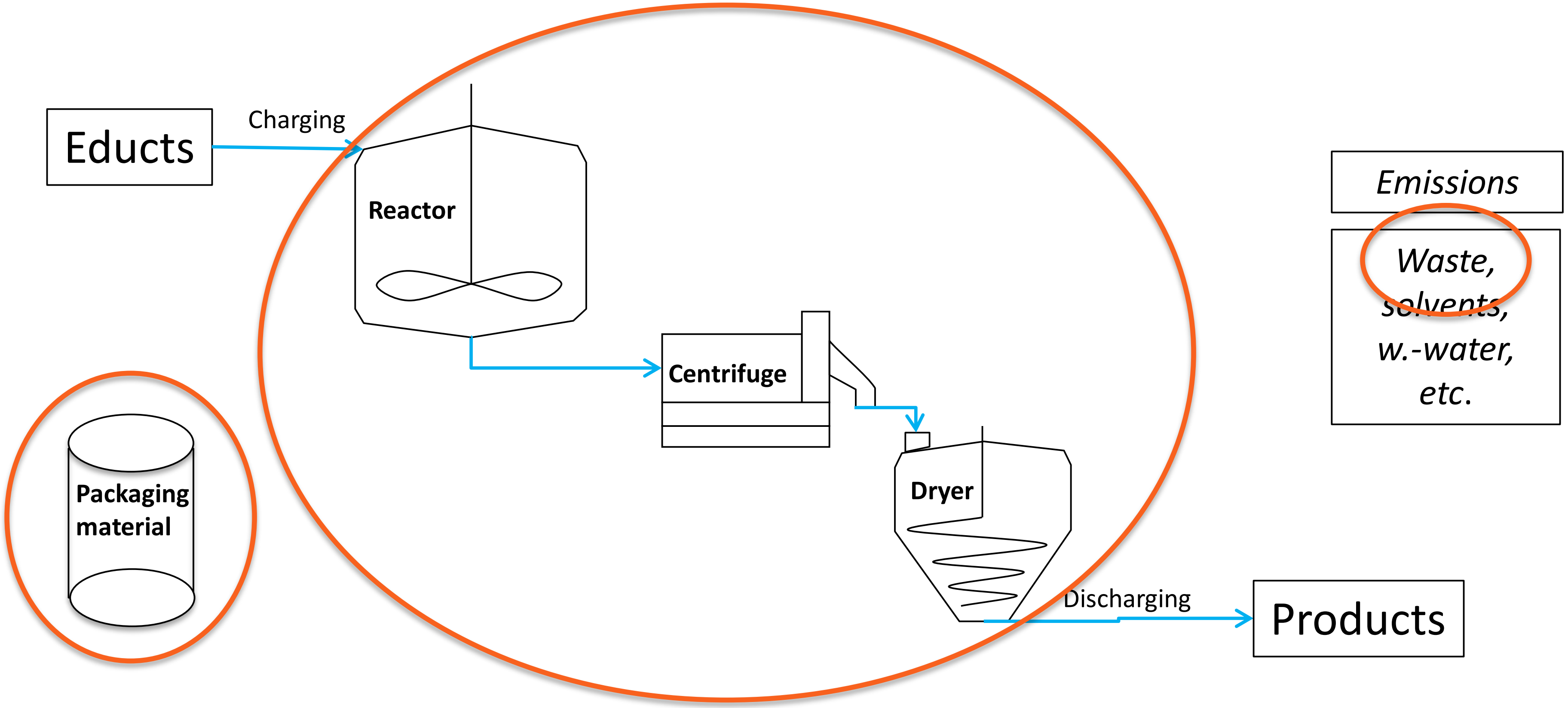
Critical interaction between the used chemicals and between chemicals and materials



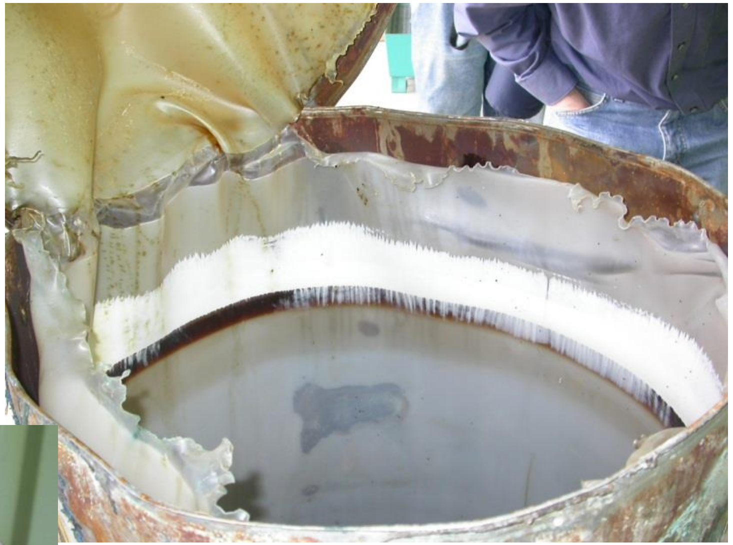
Critical interaction between chemicals and materials

- Incident in a chemical production plant
  - Due to an operational error a mixture of thionyl chloride, ethyl acetate and acetyl chloride have to be disposed of. For disposal the worker used the empty thionyl chloride drum. Short time later the drum exploded.

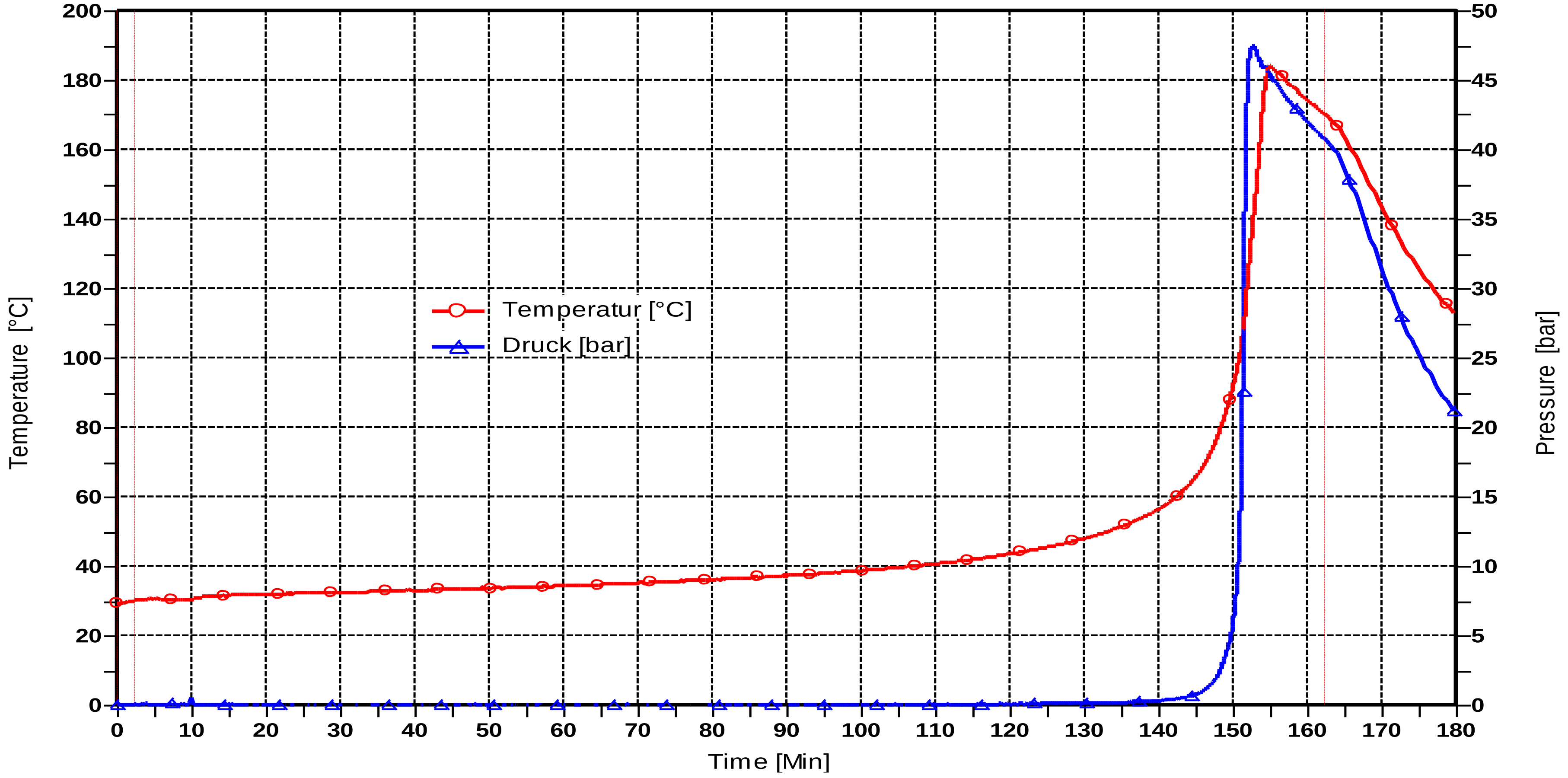
- Result of safety examination in laboratory
  - No critical reaction between thionyl chloride, ethyl acetate and acetyl chloride.
  - But, the used drum was zinc-coated
    ➔ critical reaction under pressure build-up between ethyl acetate, thionyl chloride and zinc !

Critical interaction between chemicals and materials

- Incident in a chemical production plant B:
  - In a process the excess of $POCl_3$ is distilled off and purged into a 200 l steel drum with a PE-inliner. Approx. 10 h later the drum burst.
  - Between the batches the pipes were washed with acetone. Residual quantities of acetone remained in the pipes.
- Result of safety examination in laboratory:
  - Retarded critical reaction between acetone and $POCl_3$.



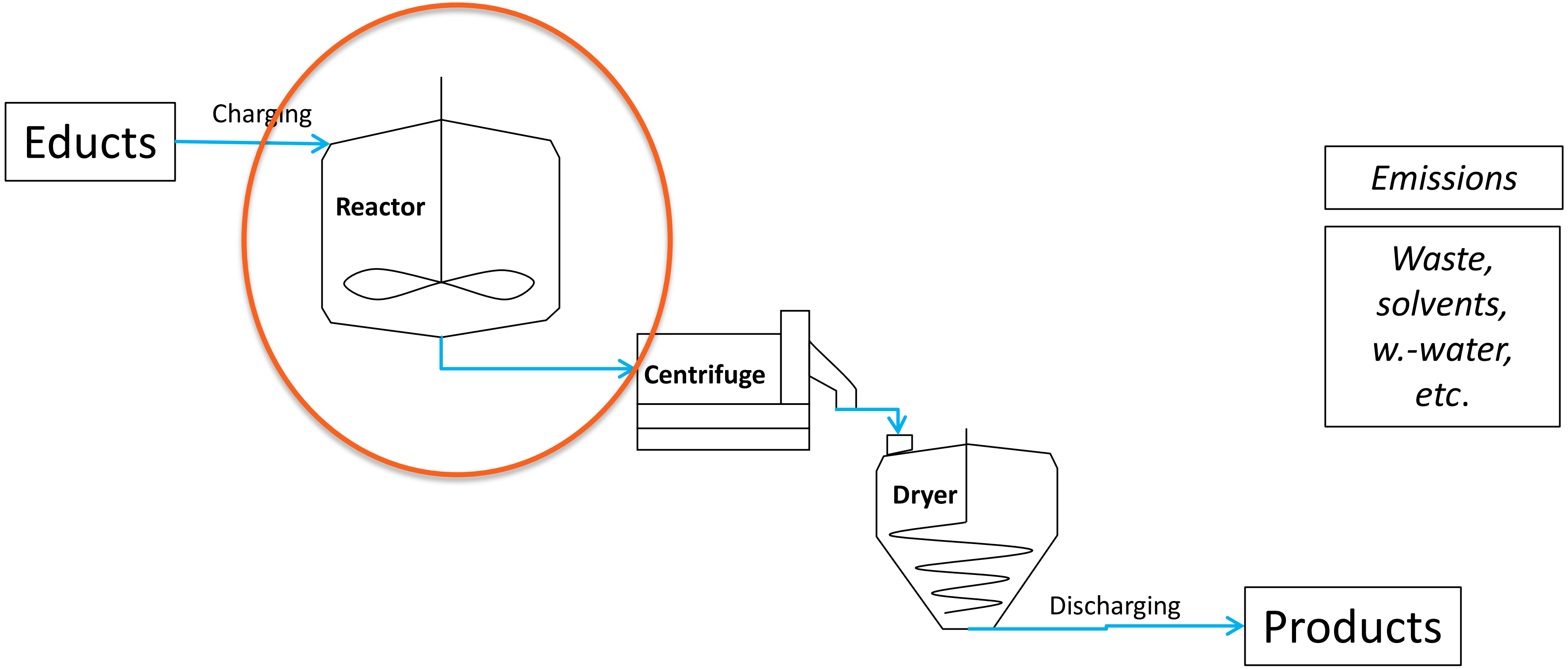
- Reaction experiment
  - closed cell test, $POCl_3$ overlay with ca. 5.8 weight-% acetone



What is necessary for a safe process?

Chemistry – chemical reaction

Calorimetric measurements for chemical reactions



Chemistry – chemical reaction

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- The chemical reaction should be known, including side reactions and consecutive reaction. The chemical reaction can depend on the reaction temperature or the working procedure.
- Mass balance of the whole reaction is very useful
- Side products can have a big influence on process safety
- Are decomposition reactions known?
- Waste streams can contain highly reactive compounds or unstable substances (e. g. slow gas generation leading to a pressure build up in waste containers)

Working procedure for chemical reaction

- Batch reaction:

All reagents are charged to the reactor.
Then the content is heated to the reaction temperature.

- The accumulation of reaction partners is at the beginning 100 %.
- For an exothermic reaction, if the cooling capacity is not sufficient, an uncontrolled temperature rise occurs and a run away reaction is possible.
- Batch reactions should only be applied with endothermic or very slow reaction with smooth exothermic behavior.

What is in general the best temperature for running a exothermic batch reaction?

The lowest possible reaction temperature is in general the safest temperature!

Working procedure for chemical reaction

- Semi-batch reaction

One reaction compound (including solvent) is charged to the reactor.
The other compound is added over a defined time at the reaction temperature.

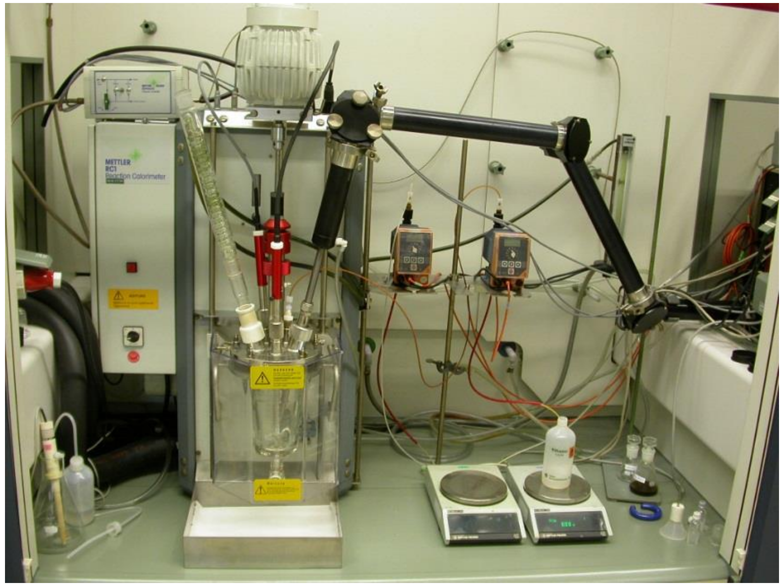
- The accumulation of reaction partners is at the beginning 0 %.
  Across the whole addition time the accumulation should be small.
- Always add the reactive compound.
  (Adding a catalyst or a compound in a huge excess is not a semi-batch process!)
- A stop of the addition stops further heat generation (if low accumulation).

What is in general the best temperature for running a exothermic semi-batch reaction?

The highest possible temperature is the best! -> fast reaction -> less accumulation

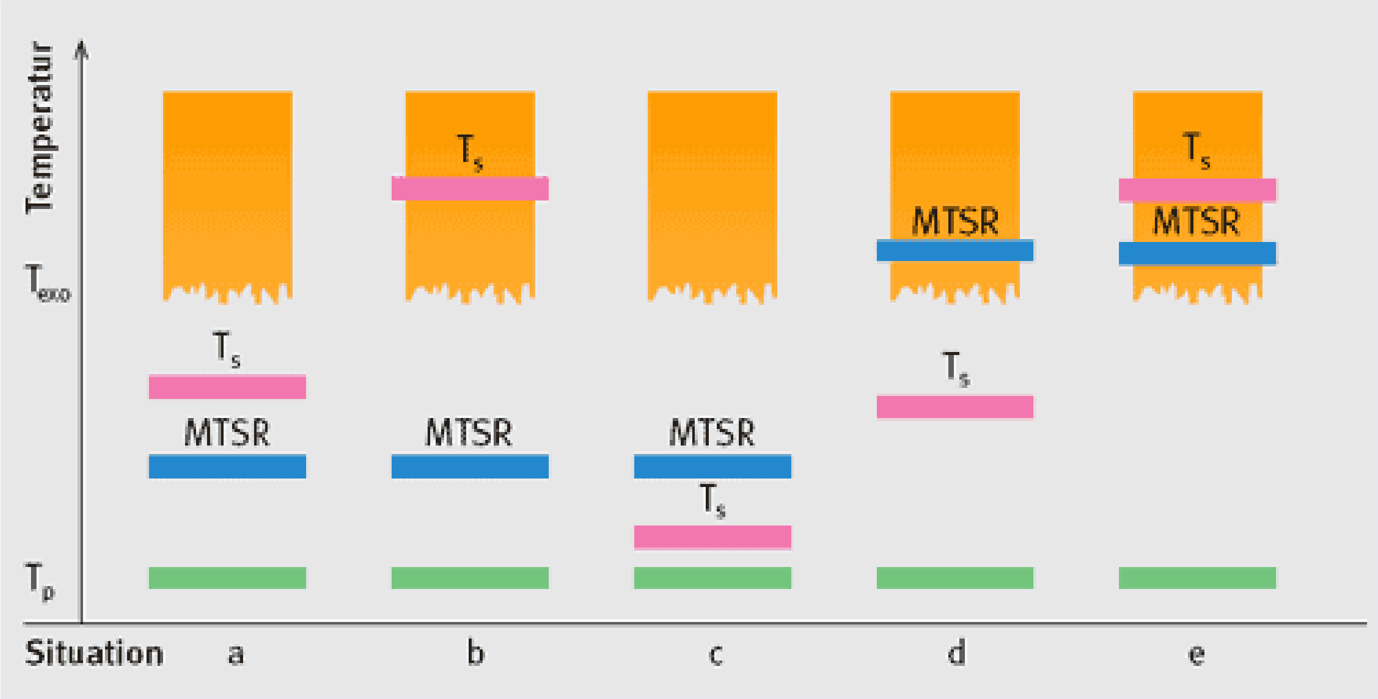
Chemical reaction parameters, calorimetric measurements

- Safety investigation of reaction under process like conditions:
  - Reaction calorimeter (e.g. Mettler RC1) with dosing, gas measurement etc.



- Determination of:
  - Heat of reaction ΔH_R [J/g] or [J/mol]
  - Heat capacity c_p [J/g K]
  - Adiabatic temperature rise ΔT_{ad} [K] or [°C]
  - Degree of accumulation [%]
  - Gas release [l/min]
- Adiabatic investigation of abnormal operating conditions:
  - Determination of thermal stability under adiabatic conditions (no heat exchange, like DTA)

Thermal hazard potential of chemical reactions



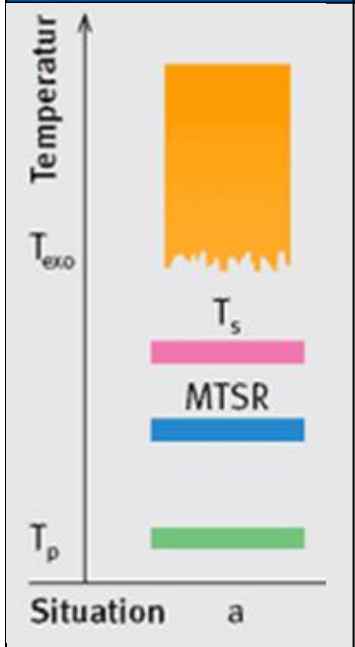
T_p : process temperature at the start of the deviation

MTSR: maximum temperature of the synthesis reaction; $MTSR = T_p + \Delta T_{ad} \cdot \alpha_{accu}$

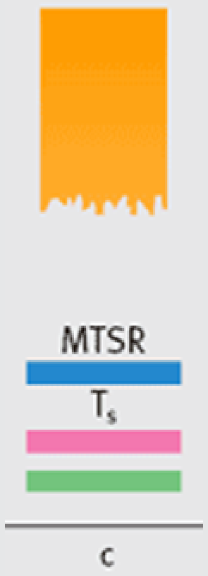
T_{exo}: the maximum temperature at which a substance or reaction mixture can just be handled safely

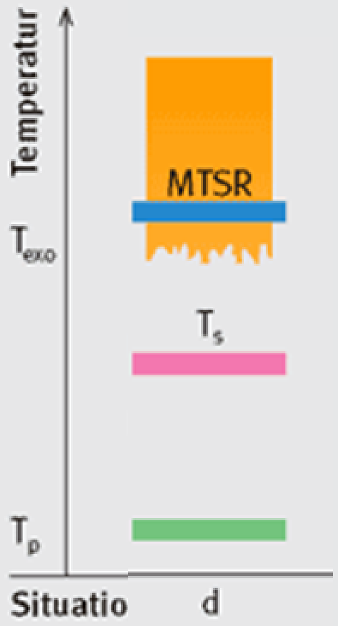
T_s: ($=T_b$) the boiling point in an open system

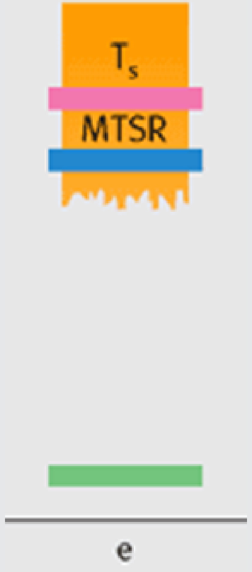
Thermal hazard potential of chemical reactions

Case	Description - criticality
	The boiling point of the mixture and the maximum reaction temperature stay below T_{exo}. Such processes may be regarded as inherently safe with respect to the process deviation evaluated.

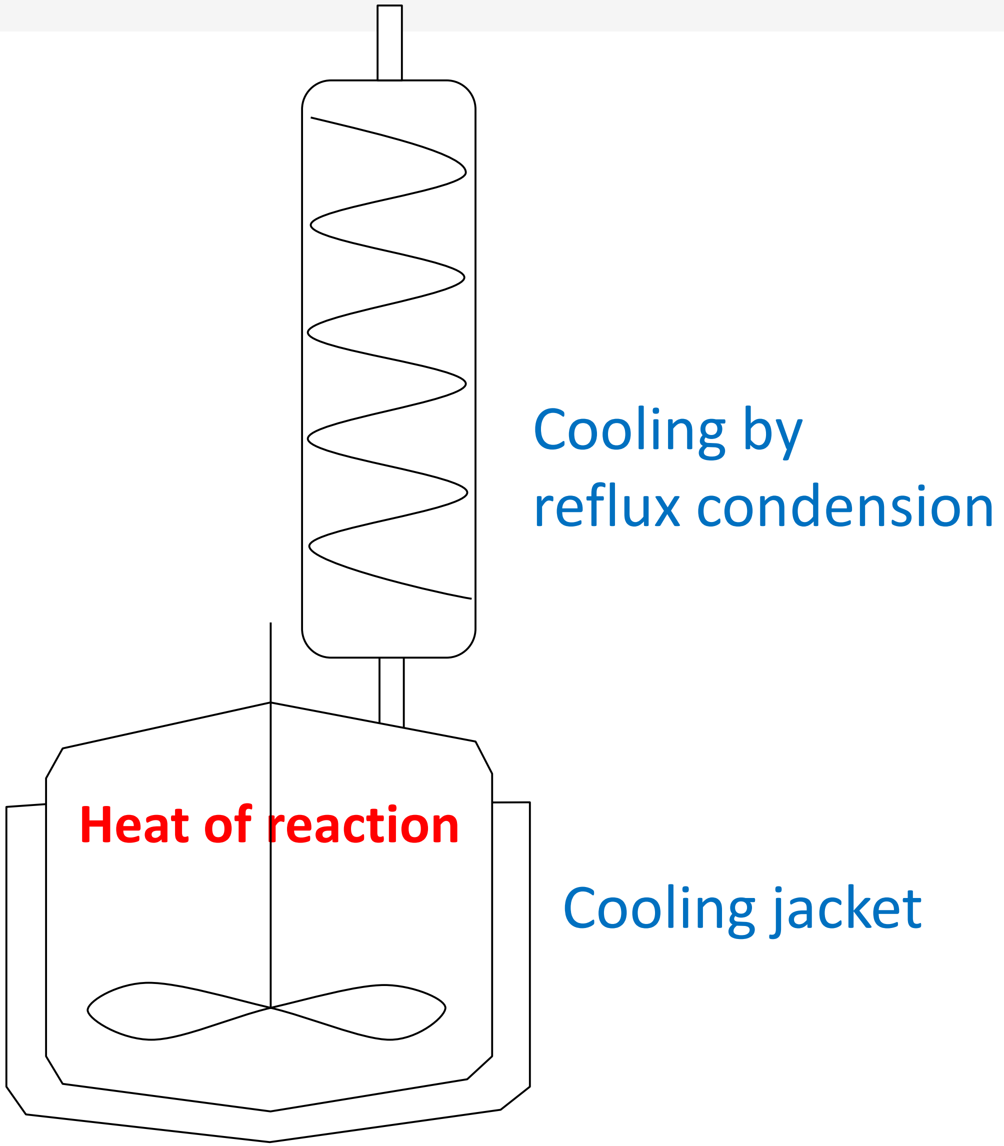
Case	Description - criticality
	Absence of the boiling point barrier, but maximum reaction temperature below T_{exo}. The process may be regarded as safe.

Case	Description - criticality
	The boiling point with its latent heat of evaporation may be considered as a safety barrier (adquate condenser!) In a closed system, the reactor must be designed for the maximum expected overpressure or be equipped with a pressure relief device. It would be better to reduce the accumulation so that the boiling point could not be reached.

Case	Description - criticality
	It must be evaluated if the evaporation capacity provides sufficient safety. If not, additional organizational or technical measures have to be implemented. If the operation is performed in a closed system, the temperature corresponding to the relief valve's set pressure may not be too high.

Case	Description - criticality
	This case must be rated as problematic. In case of a (simple) cooling failure, the reaction can pass over the safe temperature range. Plant and/or process modifications should be evaluated in such situations.

Temperature control of chemical reaction



Heat balance of exothermic reactions

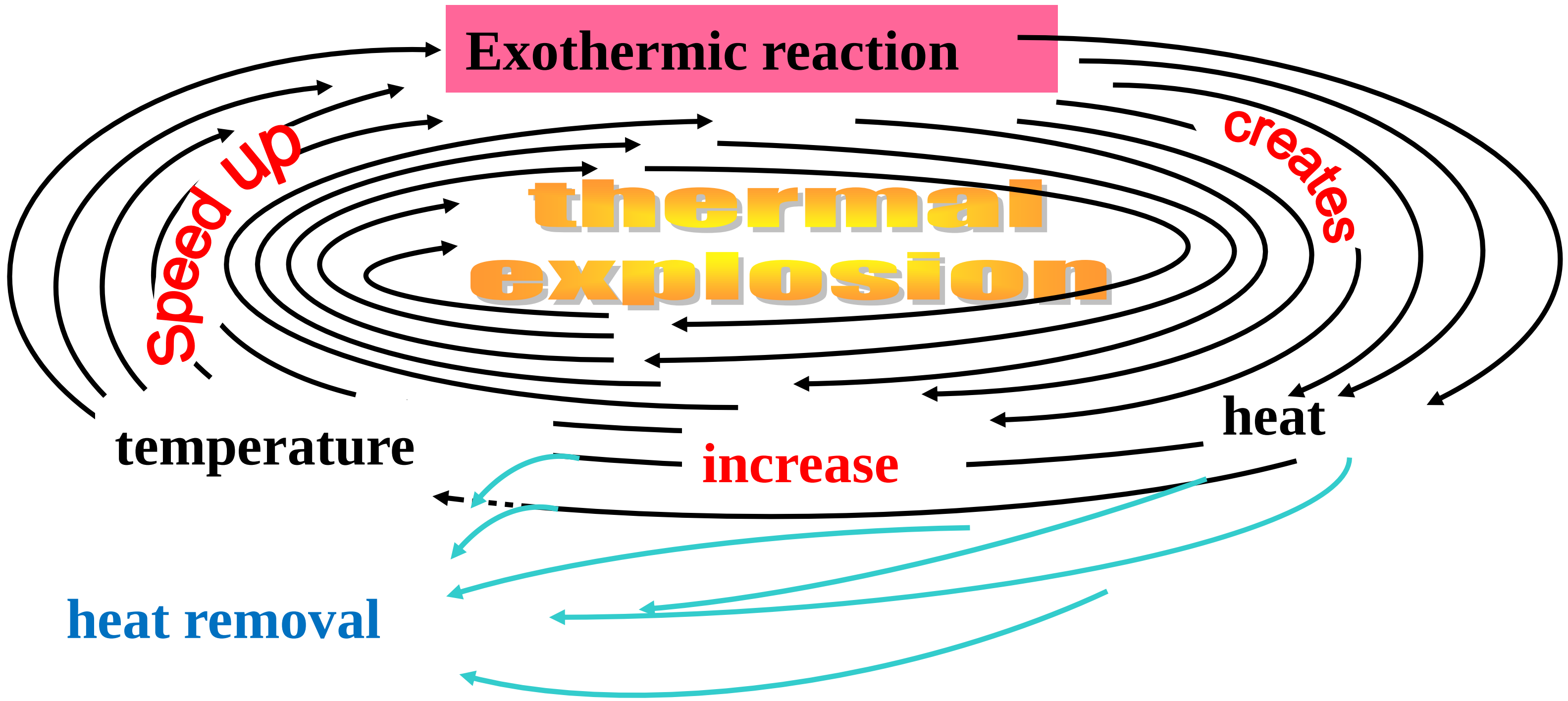
heat production

heat removal

Increased heat production	Decreased heat removal
• Additional energy supply (e.g. heating, stirring, pumping)	• Loss of cooling (e.g. pump failure, solvent evaporated)
• Higher concentration of reactants (e. g. missing solvent)	• Degrade heat transfer (e.g. fouling, adhesion)
• Presence of a catalyst (e.g. rust, nonferrous metals)	• Increase of viscosity (e.g. higher degree of polymerization)
• Initiation of other exothermic processes (e.g. side reaction, decomposition)	• Inadequate mixing (e.g. pump failure, solvent evaporated, stirrer failure)

Exothermic and run-away reaction

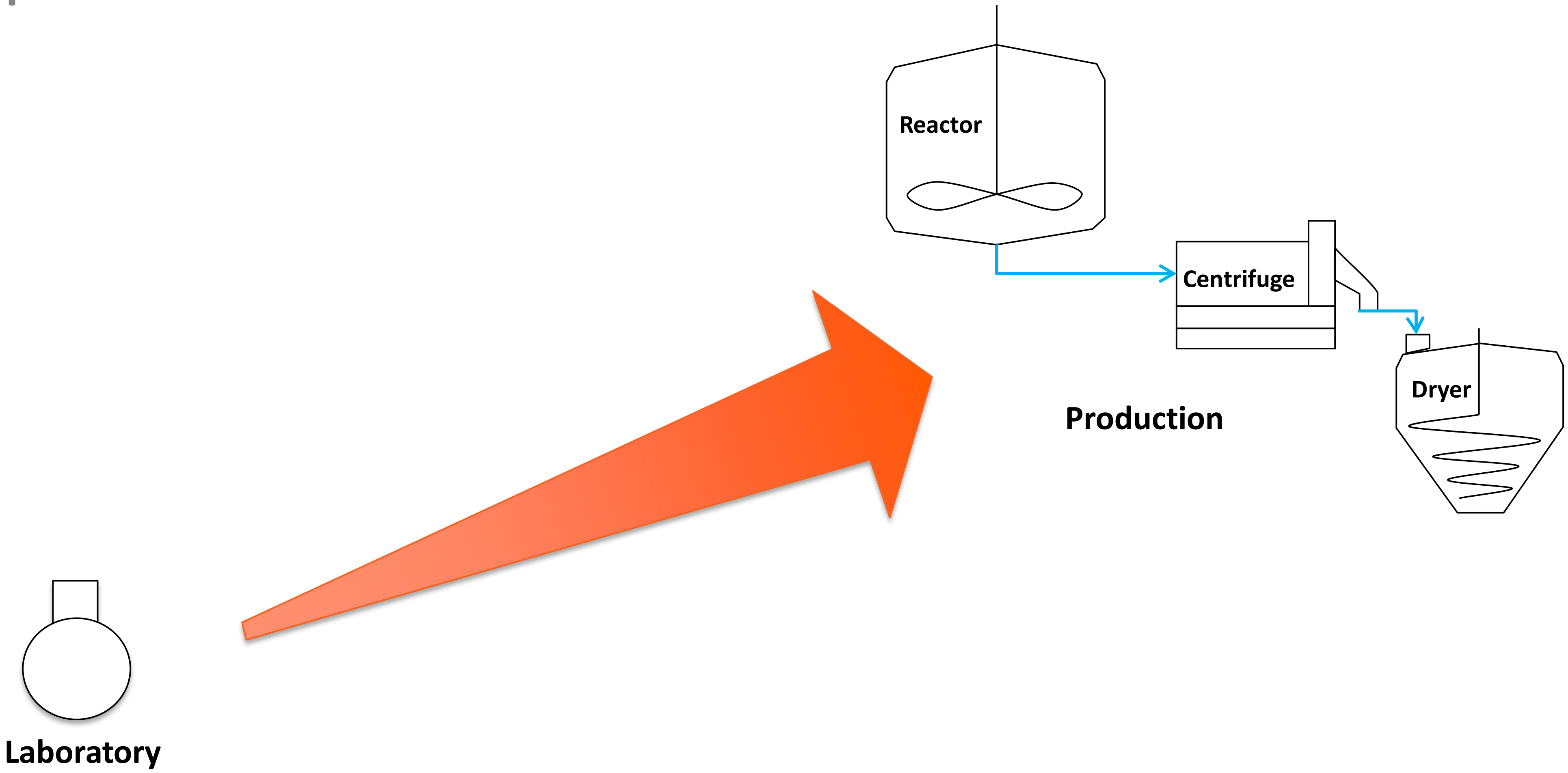
- An exothermic reaction produces heat which leads to an increase of the reaction temperature if the cooling capacity is not sufficient.
- A runaway reaction is an exothermic chemical process, which leads to uncontrollable reaction conditions due to an uncontrolled rise of the reaction speed.



Exothermic reaction and run-away reaction

What is necessary for a safe process?

Scale up



Scale up laboratory → (pilot) plant

- Example of a heat balance change during the scale up

- From laboratory (1 l) to pilot plant (1 m^3).
- Dosing controlled reaction
- Exothermic reaction
- Reaction heat of 360 kJ kg^{-1}
  (= 0,1 kWh kg^{-1})
- Density of reaction mass is 1 g cm^{-3}
- Reaction temperature 80 °C
- Filling degree is 100 %
- Heat transmission of both apparatus are 500 W m^{-2} K^{-1}
- Effective temperature difference for cooling is 30 K

Scale up – laboratory – (pilot) plant

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	Laboratory	Pilot or production plant	
Reactor size	1 l	1 m^3	Factor 1000
Cooling surface	0,046 m^2	4,4 m^2	Factor ~100
Specific cooling power	15 kW m^{-2} (= 500 W m^{-2} K^{-1} * 30 K)		
Cooling power	**0,69 kW** (= 15 kW m^{-2} * 0,046 m^2)	**66 kW** (= 15 kW m^{-2} * 4,4 m^2)	Factor ~100
Reaction power with 3 h dosing time	0,03 kW (= 0,1 kWh kg^{-1} * 1 kg /3h) *heating required*	33 kW (= 0,1 kWh kg^{-1} * 1000 kg /3h) cooling sufficient	
Reaction power with 2 h dosing time	0,05 kW (= 0,1 kWh kg^{-1} * 1 kg /2h) *no cooling required*	50 kW (= 0,1 kWh kg^{-1} * 1000 kg /2h) cooling sufficient	
Reaction power with 1 h dosing time	0,1 kW (= 0,1 kWh kg^{-1} * 1 kg /2h) cooling sufficient	**100 kW** (= 0,1 kWh kg^{-1} * 1000 kg /1h) **cooling insufficient**	

Expectation of an EHS auditor

R&D → scale up → production

Amounts of substances	Location	Working documents	Guidance documents
miligrams to grams	Research & Development Laboratory	- Lab documentation - First observations to process safety	- Policy „Safe Research & Development“ - Lab safety SOPs
grams to kilograms	Transfer from tab to kilolab / pilot plant	- Basic safety report - Transfer report	- Regulation to „Basic safety examinations“ - Transfer protokoll
kilograms	kilolab / pilot plant	- Batch records - Safety assessments - Process safety examinations	- Guidelines for safety examinations - SOPs to substance handling etc.

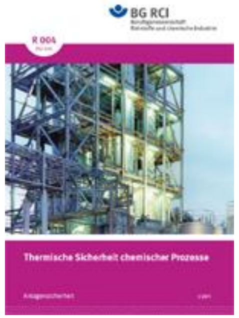
Expectation of an EHS auditor

R&D → scale up → production

Amounts of substances	Location	Working documents	Guidance documents
kilograms to tons	Transfer from pilot plant to production	- Transfer report - Risk assessment - Technical measures	- Transfer protokoll - SOP „Risk assessement/ HAZOP“
kilograms to tons	Production plant	- Batch records **- Change Control documents** **- Maintenance of technical installation**	- SOP „ CC“ - SOPs „Maintanance“
kilograms to tons	Transfer to other plants	- Transfer report - Risk assessment - Technical measures	- Transfer protokoll

- https://www.bgrci.de/fachwissen-portal/topic-list/hazardous-substances/
- https://downloadcenter.bgrci.de/resource/downloadcenter/downloads/R003e_Gesamtdokument.pdf

Accident Prevention & Insurance Association - data sheets
[BG-Merkblätter R 001-007]



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PSCI Auditor Training 2018

Runaway Reaction Explosion
(taken from a presentation by Lamy Bao)

PSCI Questionnaire & observations

Dr. Stefan Gries
Boehringer Ingelheim Corporate Center, Corp. EHS&S

TRAINING STRUCTURE

1. Session 1
   - Process safety parameters
   - Essential information to chemical processes
   - Critical interactions of material
   - Exothermic and run-away reaction
   - Scale up

2. Session 2
   - Runaway reaction
   - PSCI Questionnaire & Typical Observations

3. Audience questions & discussions

Investigation Video

Runaway Reaction Explosion

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- **T-2 Labs , Jacksonville, Florida (USA)**
- **Video 1**
- **Video 2**

Investigation Video

Runaway Reaction Explosion

Investigation Video

Runaway Reaction Explosion

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Investigation Report - Explosion in T-2 Labs

- **Location: Jacksonville, Florida (USA)**
- **Incident: Explosion in Reactor due to runaway reaction**
- **4 employees killed, 32 injured (including 28 from surrounding community**
- **Explosion force: Equivalent to 1,400 lbs of TNT (≈ 635 kg TNT)**
- **Causes:**
  - **Company did not recognize the worst credible scenario**
  - **No redundancy in cooling system**
  - **Inadequate pressure relief device**

Reaction Hazards - Historical Data of Incidents

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(Ref. Book: Chemical Reaction hazards by John Barton)

Following data was collected for 189 industrial incidents in UK involving thermal runaway reactions:

- **134 incidents were classified by processes, key ones are:**
  - **Polymerization (condensation): 64 (48%)**
  - **Nitration: 15 (11 %)**
  - **Sulphonation: 13 (10%)**
  - **Hydrolysis: 10 (7%)**
  - **Raw Materials Quality: 15 (11%)**
  - **Others: 13%**
- **34 incidents were caused because there was no study done for reaction hazards**

Reaction Hazards – Incidents by Causes

(Ref: Book: Chemical Reaction hazards by John Barton)

- **35 incidents were caused by mischarging of reactants or catalysts (29%)**
- **32 incidents were caused by temperature control (27%)**
- **25 incidents were caused by maintenance (21%)**
- **17 incidents were caused by agitation (14%)**
- **11 incidents were caused by human error (9%)**

PSCI questionaire for Process Safety

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Audit Questions Summary – Process Safety

Topic	Question summary
Process Safety	76: Top 3 most hazardous process activities conducted at this facility 77: Process hazard assessment 78: Evaluated the impact of its operation on the community Evaluated the impact from the activities of neighboring businesses 79: Risk assessment for explosion of flammable liquids, vapors, powders, and gases 80: Preventive maintenance of safety relevant equipment. 81: Handling compressed gases safely 82: Bulk chemical handling procedures 83: Safety measures around direct fire equipment (e. g. boiler, incinerators, ovens etc.)

Process Safety - Typical Observations

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77	Does the facility perform Process Hazard Assessment (PHA)? *Aim is to identify processes or operations that could present significant risks in case of deviation (exothermic reactions, use of flammable, combustible or toxic materials, processes involving extreme temperatures or pressures).*	… • Collection of process information (process safety data, design information, operating parameters, and equipment specifications) • Hazard evaluations capturing significant risks during process development, preliminary engineering, and upon completion of process design? • Sizing of pressure vessels and relief devices according to appropriate codes and standards? • Flammable storage areas separate from production and well managed?

No safety data for any chemical reaction are available (example: heat of reaction, adiabatic temperature rise, decomposition temperature,…)
The auditee has made some improvement to collect process safety data and to conduct PHA for high sophisticated chemical reaction (nitration, oxidization, hydrogenation etc.) running at site. Nevertheless the interpretation of this data and the transfer into safety measures for the production is not always reliable.
Basic safety data for chemical processes are available from the Development report. However data are archived and in case of changes these data are not any more reconsidered, since there is no systematic approach in place to cover chemical safety data in a change control system.

Process Safety - Typical Observations

Most of the vent pipes coming from safety valves or rupture disks have at least 3 ninety degree angles. Therefore there is no evidence about the pressure profile inside the venting pipe. This leads to back pressure build up in case of activation with a certain risk for pipe bursting.
The reactor where the bromination takes place misses a safety valve or rupture disc respectively. Furthermore the adiabatic reaction heat is not known.
The explosion vent of the fluid bed dryer in the Bromhexine clean rooms is venting into the cleanroom.
In the chemical production building, the venting pipes of the safety valves end close to the floor in the production room. Taking into consideration the highly hazardous nature of the ingredients (e.g. Oleum, CO, SO_3) this may lead to fatal accidents in case of a pressure relief.

Process Safety - Typical Observations

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79	Does the facility perform risk assessment related to the explosion of flammable liquids, vapors, powders, and gases in processing operations (including storage, transfer and charging)? Does it include the following steps?	• Assessment of the hazards (Minimum Ignition Energy, Kst classification rating, Impact sensitivity etc.) of the handled combustible dusts and powders • Hazardous area classification (zones according EU-ATEX and Classes according to US-NFPA) … • Installation of special electrical equipment for flammable vapors, gases, combustible dusts, … • Periodic testing of grounding and bonding circuits, lightning arresters, and electrical distribution equipment? • Maintenance/calibration done for critical safety equipment (e.g. sensors, instruments, valves, interlocks, reactors, condenser etc.) at suitable intervals. • Assessment of the hazards due to mechanical ignition sources? • Installation of special electrical equipment for flammable vapors, gases, combustible dusts, and wet areas? • Periodic testing of grounding and bonding circuits, lightning arresters, and electrical distribution equipment? • Maintenance/calibration done for critical safety equipment (e.g. sensors, instruments, valves, interlocks, reactors, condenser etc.) at suitable intervals. • Assessment of the hazards due to mechanical ignition sources?

Process Safety - Typical Observations

Safety data like MIE, St Class etc. are available for most of the finished products (API). No data is available for isolated intermediates. Hence it could not be proven if the Fluid Bed Drying of intermediates can be done safely.
The company has not assessed the hazards (Minimum Ignition Energy, K_{st} classification rating, Impact sensitivity etc.) associated with combustible dusts and powders being handled in various operations at site.
At the installations in the production area stainless steel clamps were installed instead of using copper wires for grounding and bounding. No evidence was provided showing that this type of bounding grounding is as safe and effective as copper wires.

Process Safety - Typical Observations

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The Customer product is received in packaging, treated in anti-static agents and the specifications for the finished product require it to be packaged in liners that are treated with anti-static agents. However, the material handled in the intermediate steps is not treated with anti-static agents. Site personnel assume that the minimum ignition energy is low enough to warrant this type of packaging if the incoming and finished product are packaged in anti-static treated liners.
There is no gas detector near the ethanol recovery device at VB1 workshop, no O2 detector at centrifuges which used N2.
In the production plant, grounding points and grounded piping are installed. A detailed SOP for working in Ex-zones is available and trained. But an instruction, how to ground mobile equipment (e.g. solvent drums) is not included in this SOP.
An Ex light in the hydrogenation room was labeled as "Ex ed IIB T4", which was not the proper type for hydrogen environment.

Process Safety - Typical Observations

80	Describe how the facility ensures preventive maintenance of safety relevant equipment.	• Pressure safety relief valves/rupture disks • Bonding/earthing systems • Mass transfer systems (e.g. piping systems) • Pressurized vessels • Explosion prevention system (e.g., prevention of static electrical discharge) • Is there emergency power supply for relevant equipment?

Anti-static bridge connection of pipes for transporting flammable chemicals is very rusty in Building A-6.
Most of the P+IDs presented during the audit where not up to date. Furthermore the guidelines of ISO14617 regarding the symbols are not followed. P+IDs should always be up to date, showing the "as build" situation to avoid any risk due to mistaken identity of any component of an equipment.

Process Safety - Typical Observations

81	Does the facility provide a means for handling compressed gases safely that includes:	Inspection and approval before acceptance of delivery? Storage in a segregated area designed for compressed gases? Separation or barriers to manage compatibility issues? Gas classification labeling? Regulator, hose and flexible connection inspections?

PSCI Questionnaire

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82	Has the facility developed and implemented bulk chemical handling procedures that include:	Not applicable Specific unloading and loading procedures? Identification sampling before unloading? Hose inspection? Fire protection? Spill control measures (dike or bund area)?

Storage of Oxalyl Chloride is done under “normal” conditions (Hyderabad room temperature in the warehouse). As of the “Tech Pack” information, the storage temperature should not exceed -10°C. Even if there are some newer SDS available that storage at middle European room temperature range (max. 25°C) might be sufficient, the company could not show evidence that the change of storage conditions was assessed.
The bulk unloading process needs improvement. The unloading area is asphalt but no defined retaining volume in case of any spillage is provided.

Process Safety - Typical Observations

83	What are the safety measures around direct fire equipment (e. g. boiler, incinerators, ovens etc.)? *Consider gas accumulation, steam overpressure...*	

In the Building B, Water For Injection (WFI) system, the clean steam generator operates at 65 psig with a safety relief valve venting directly to the room. In the case of activation, 155°C steam would be released and fill the room.

PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

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PSCI Auditor Training 2018

Environmental Protection

Birgit Mertens

Birgit Mertens

Johnson & Johnson

Sr. Principal Environment (Global Subject Matter Expert)

Career History:

Head of Environment Janssen Campus Belgium (Pharmaceutical manufacturing /R&D sites) (2012-2015)

Head of Environment Janssen API Small Molecule manufacturing Belgium (2007-2012)

Head of Environmental Laboratory Janssen Belgium (2006-2007)

Since 2006 part of J&J PIE strategy development

TRAINING STRUCTURE

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Agenda

1. Auditor insights
2. Audit overview – SAQ/Audit tool questions review with auditor guidance
3. Deep dive – Pharmaceuticals in the Environment
4. Example audit findings
5. Audience questions

1. AUDITOR INSIGHTS

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Preparation is Key

- Supplier website & SAQ
- Internet
- Google satellite imagery

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- Overview presentation – supplier
- Site tour expectations – be specific
- Documents
- Permission to photograph
- Neighbours

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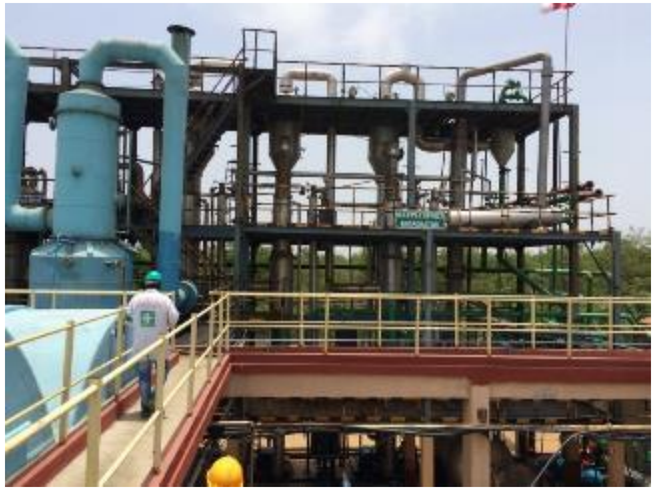
First Impressions Count !!!

Particularly look for the following:

- Surface water
- Storm drains
- General housekeeping
- Excavations for construction
- Storage or placement of waste materials exterior to the facility
- Evidence of releases
- Visible emissions from air emission sources
- Significant dead vegetation (not seasonal)

Interior Tour should include:

- Boilers and Diesel Generators
- Fuel storage areas
- Wastewater collection and treatment systems
- Stormwater collection and discharge systems
- Waste storage areas



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Interior Tour should also include:

- Process areas
- Water extraction wells
- Potable water delivery and storage systems
- Deep wells or borings for waste or wastewater disposal
- Underground storage tanks
- Air pollution control equipment for boilers and process emissions
- Solvent storage and recovery
- Incinerators

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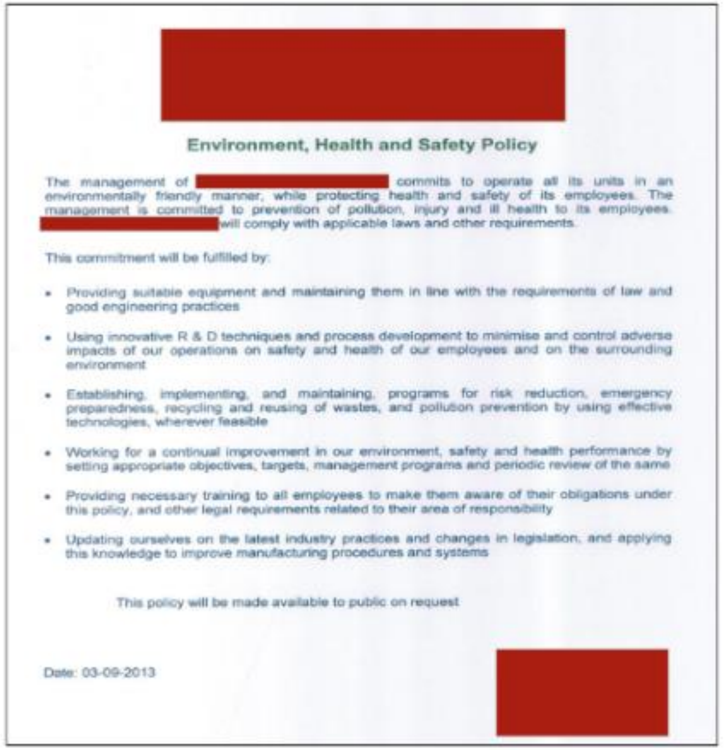
Audit Questions Summary – Environmental protection

Topic	Question summary
General	• Written environmental policy, procedures, and practices • Environmental objectives or goals for performance improvement, including metrics and targets • If in a water scarce region, is there a water strategy
Chemical registrations	• Is the site affected by any chemical registration program (REACH etc.)
Environmental Authorizations	• Environmental permits or authorization
Waste and Emissions	• Process to manage third-party waste treatment and disposal • Waste disposal methods & locations (explain as applicable) • Process wastewater management • Types of air emissions • Hazardous chemicals (including APIs) management program • Storm water management practices
Spills and releases	• Hazardous materials transportation • Soil, surface water or groundwater contamination • Potential environmental risks from hazardous substances

General		
31	Does the facility have written environmental policy, procedures, and practices?	Policy: Yes No Procedure: Yes No Comments: Please provide a copy of the policy and a list of procedure titles.

- Ask for the supplier's environmental, health and safety policy.
- How are people trained in it?
- Are procedures in place for environmental activities?
- Do the operating procedures include environmental aspects?
- Is there clear evidence that the procedures are followed?
- During personnel interviews, are they familiar with the environmental policy, procedures & practices?


[redacted]

Environment, Health and Safety Policy

The management of [redacted] commits to operate all its units in an environmentally friendly manner, while protecting health and safety of its employees. The management is committed to prevention of pollution, injury and ill health to its employees. [redacted] will comply with applicable laws and other requirements.

This commitment will be fulfilled by:

- Providing suitable equipment and maintaining them in line with the requirements of law and good engineering practices
- Using innovative R & D techniques and process development to minimise and control adverse impacts of our operations on safety and health of our employees and on the surrounding environment
- Establishing, implementing, and maintaining, programs for risk reduction, emergency preparedness, recycling and reusing of wastes, and pollution prevention by using effective technologies, wherever feasible
- Working for a continual improvement in our environment, safety and health performance by setting appropriate objectives, targets, management programs and periodic review of the same
- Providing necessary training to all employees to make them aware of their obligations under this policy, and other legal requirements related to their area of responsibility
- Updating ourselves on the latest industry practices and changes in legislation, and applying this knowledge to improve manufacturing procedures and systems

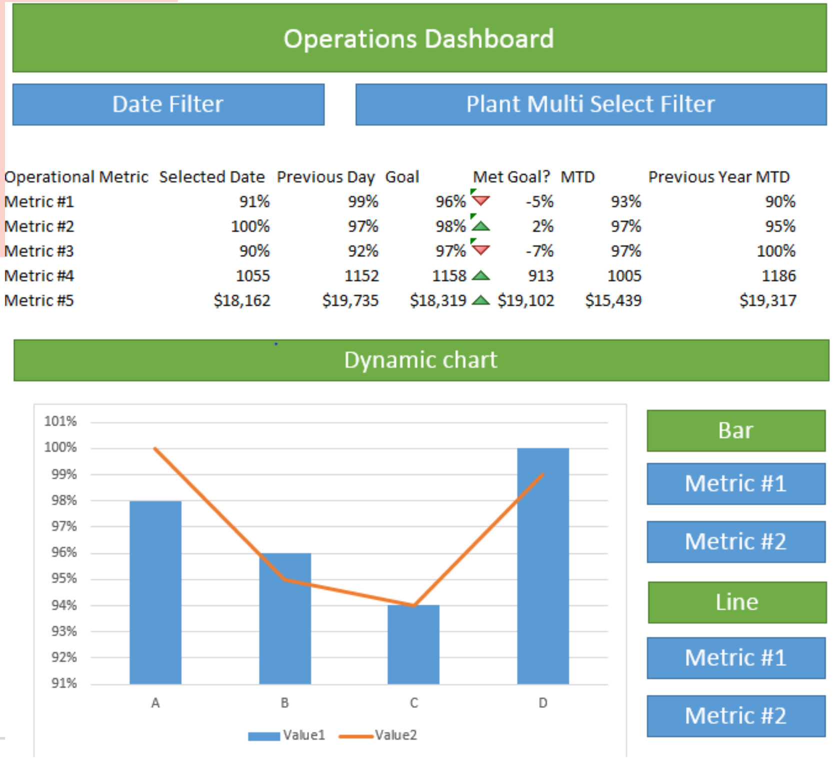
This policy will be made available to public on request

Date: 03-09-2013

[redacted]

32	Does the facility have documented environmental objectives or goals for performance improvement, including metrics and targets?	Yes No If yes, please describe goals, metrics, and/or targets and any improvements made in last 3 years.: Do tracking and reduction programs exist for the following impacts: Energy consumption: Water consumption: Amount of hazardous waste: Amount of non-hazardous waste: Greenhouse gas emissions: Does the facility publicly report data? Yes No Program description: If yes, where can the information be found:

- Does the facility have clear environmental goals?
- Are they set locally or at the corporate level?
- Is there clear support for achieving the goals?
- Review the methods that facility has in place to measure key environmental impacts



33	If the site operates in a water scarce region, has the facility developed a long-term strategy for future water sourcing and management?	Yes No NA Please explain: Is the long-term continuity for future water sourcing and management already covered in the site-based Business Continuity Management plan? Yes No NA Please explain: Does the facility have an authorisation/permit for water intake from groundwater, river or a public system? Yes No NA Please explain: Does this authorisation/permit have any requirements that will restrict or stop your ability to obtain water? Yes No NA Please explain:

- Describe any fresh water availability, access or infrastructure issues the site may be facing locally or regionally.
- Is the water withdrawal from groundwater from a renewable/sustainable source (not depleting the groundwater source)?
- If the site is reliant on a municipal water system, does the site know if the municipality will be unable to capture and distribute adequate supplies of water due to infrastructure development issues or lack of institutional capacity to maintain and manage them appropriately?

[1] Water scarcity is defined by the UN Food and Agriculture Organization as: (i) scarcity **in availability** of fresh water of acceptable quality with respect to aggregated demand, in the simple case of physical water shortage; (ii) scarcity **in access** to water services, because of the failure of institutions in place to ensure reliable supply of water to users; (iii) scarcity due to the **lack of adequate infrastructure**, irrespective of the level of water resources, due to financial constraints. In the last two cases, countries may have a relatively high level of water resources endowment but are unable to capture and distribute them because of limited financial resources for infrastructure development or lack of institutional capacity to maintain and manage them appropriately. (UN FAO, http://www.fao.org/nr/water/topics_scarcity.html)

Audit Overview

Chemical Registrations		
34	Is the site affected by a chemical registration program such as EU REACH (Registration, Evaluation; Assessment, Authorization and Restriction of Chemicals), China REACH, or TSCA (Toxic Substances Control Act) which requires registration or authorization to import or use a specific compound?	Yes No NA If yes, please identify the program: In case of yes, do you have a process in place to comply with the regulation? Yes No NA Which materials are applicable? • Finished Products produced in the site • Raw materials used for finished products • Other
35	Do you send materials to a region where REACH or similar regulations apply?	Yes No If yes, how do you ensure compliance in this region and what is your role in this case?

Audit Overview

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

Environmental Authorizations		
36	Does the facility have the required environmental permits or authorizations?	Yes No NA If yes, please list the permit type, the name of the permit, and the expiry date: NOTE: Please have all required environmental permits, licenses, information registrations and restrictions available for review including supporting compliance documentation.

Describe the permits and list the permit # or name, confirm expiry date and compliance conditions, if there were any non-compliances within last 3 years. Also add which data was reviewed for permits, for example, waste water sampling results for flow, BOD, pH, etc.

Confirm that all commercially manufactured products are endorsed in the site permits/permit applications.
For R&D suppliers in China, EIA permit at pilot scale does not need to specifically list the products.

What mechanisms does the site use to track compliance against the permit or authorisation conditions?

List all reportable and non-reportable non-compliance with permits (and parameters) within last 3 years.
Review compliance history via web search
Review compliance history with the site during the visit including:
Status of authorisations | Any notices of violation | Any fines or penalties for non-compliance | Any spills or unplanned releases

Describe any permits specifically regulate Active Pharmaceutical Ingredients (especially antibiotics)? For example, wastewater limits, waste disposal requirements).

If site handles antibiotics, indicate the applicability of any permit conditions for managing or controlling waste streams, wastewater or biosolids/biomass from that contain APIs.

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

Waste and Emissions		
37	Does the facility have a process to select and manage third-party waste treatment and disposal facilities and service providers?	Yes No NA What records or documentations of waste disposal are maintained: Please provide specific details on land filling of waste (categories and volumes):

Check records/supporting documents such as manifests or shipping records, supplier selection procedure, contracts, audits of waste vendors, etc.

Indicate any non-compliance(s) for the site or contracted waste management supplier.

Describe assurances that waste disposal contractors possess authorizations /certifications from regulatory authorities to manage specific waste streams in accordance with local regulations and that containment and monitoring programs are in place.

Describe selection process review for the use of third-party waste facility or provider. Does it include considerations for staffing and API residual management?

Are the third-party waste treatment vendors used by the facility approved by regulatory authorities? How does the site know that they have valid Environmental permits?

How are third-party waste vendors reviewed periodically for their HSE performance/compliance?

How are waste manifest/transfer record systems followed and maintained for disposal of wastes as per applicable regulations?

More on Waste Management Disposal

- Waste must be disposed at authorized disposal facilities.
- Confirm locations of disposal
- Tracking system for waste shipments and shipment records retention
- Review hazardous waste manifests

More on Waste Management Vendor Considerations

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

- Does the facility audit their waste vendors?
- Do they have the right authorisations?
- Determine frequency, audit protocols, auditor qualification
- What is described in the contract?

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

38	Does the facility use any of the following waste disposal methods & locations (explain as applicable)? Include explanation of how hazardous, including API containing waste (e.g. antibiotics), biohazardous, fermentation biomass, non-hazardous waste is disposed of.

Onsite vs. offsite disposal
Methods: Incineration (energy recovery?), landfill (hermetically sealed?), deep well, land application, other/reuse/recycling

Describe any criteria prescribed, established or referred to for determining the disposal pathway and whether compliance can be demonstrated

Comment on the appropriateness of waste disposal via methods reportedly used with focus on high risk disposal such as land application, deep well injection, or landfill of hazardous waste. Review in detail treated wastewater and/or sludge/fermentation biomass applied to land for irrigation and/or fertilizing purposes that might include API residual.

List any vendors or relevant authorities for disposal methods or records that were reviewed.

Does this disposal method cover any of the following?
- Branded materials
- API/drug product residuals
- Biosolids, biomass or sludge containing API
- Are environmental impacts from API residuals considered?

More on Waste Management Identification, Characterization, and Inventory

FORMAT FOR MAINTAINING RECORDS OF HAZARDOUS WASTES BY THE OCCUPIER OR OPERATOR OF A FACILITY

1. Name and address of the occupier or operator of a facility :
2. Date of issuance of authorisation and its reference number :
3. Description of hazardous waste :

Physical form with description	Chemical form	Total volume (m³) and weight (in kg.)

4. Description of storage and treatment of hazardous waste :

Date	Method of storage of hazardous wastes	Date	Method of treatment of hazardous wastes

Schedule I
[See rules 3 (1)]

List of processes generating hazardous wastes

S.No.	Processes	Hazardous Waste *
26.	Production or industrial use of synthetic dyes, dye-intermediates and pigments	26.1 Process waste sludge/residues containing acid or other toxic metals or organic complexes 26.2 Dust from air filtration system
27.	Production of organo-silicone Compounds	27.1 process residues
28.	Production/formulation of drugs/pharmaceuticals & health care product	28.1 Process Residues and wastes 28.2 Spent catalyst/spent carbon 28.3 Off specification products 28.4 Date-expired, discarded and off-specification drugs/medicines 28.5 Spent organic solvents
33.	Disposal of barrels containers used for handling of hazardous wastes chemicals	33.1 Chemical-containing residue arising from decontamination. 33.2 Sludge from treatment of waste water arising out of cleaning/disposal of barrels/containers 33.3 Discarded containers/barrels/liners contaminated with hazardous wastes/chemicals
34.	Purification and treatment of exhaust air, water & waste water from the processes in this schedule and common industrial effluent treatment plants (CETP's)	34.1 Flue gas cleaning residue 34.2 Spent ion exchange resin containing toxic metals 34.3 Chemical sludge from waste water treatment 34.4 Oil and grease skimming residues 34.5 Chromium sludge from cooling water
35.	Purification process for organic compounds/solvents	35.1 Filters and filter material which have organic liquids in them, e.g. mineral oil, synthetic oil and organic chlorine compounds 35.2 Spent catalyst 35.3 Spent carbon
36.	Hazardous waste treatment processes, e.g. incineration, distillation, separation and concentration techniques	36.1 Sludge from wet scrubbers 36.2 Ash from incineration of hazardous waste, flue gas cleaning residues 36.3 Spent acid from batteries 36.4 Distillation residues from contaminated organic solvents

- The site should have a documented process to identify and properly characterize all of its waste streams
- An inventory of wastes generated should be available on site
- The inventory should include at a minimum:
  - Point of Generation (process generating the waste)
  - Hazardous characteristics and classification (corrosive, flammable, radioactive, etc.)
  - Annual Generation Rate

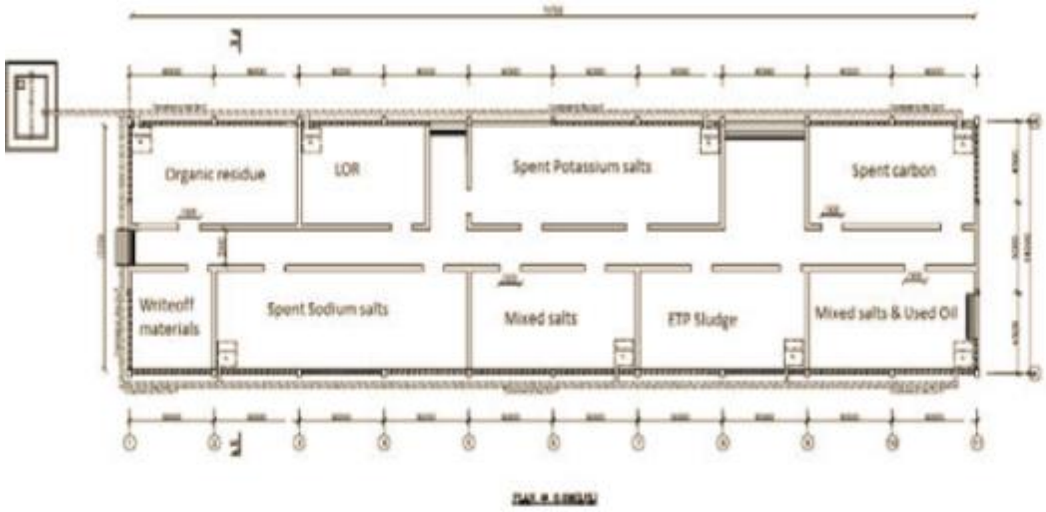
More on Hazardous Waste Management Storage and Handling

- Waste storage areas should be secured and managed
- Located indoors or in covered
- Impervious floors with secondary containment
- Storage areas clean and free of debris and accumulated liquids
- Sufficient aisle space

More on Hazardous Waste Management Storage and Handling

Review the following:

- Inspection program
- Separate storage for incompatible wastes
- Suitable emergency response equipment in place
- Suitable PPE available for personnel managing waste
- Proper security and signage



More on Waste Management Bio-Medical Waste

- Confirm with the site if they generate biohazardous wastes (e.g., microbiological testing wastes)
- Review storage and handling methods
- Must be managed appropriately while on site
- Segregated from other hazardous wastes
- Confirm disposal method and location
- Incinerated at an approved location

39	Indicate which methods are used to manage process wastewater from this facility.	Check all that apply to treatment and disposal of wastewater: • Pretreatment of process water Yes No Please describe method(s) (example – hydrolysis with caustic or heat pre-treatment): • On-site wastewater treatment: Yes No Please describe: Does the facility collect, store, and analyze samples? Wastewater? Yes No Sludge? Yes No • Discharge to an offsite treatment facility: Yes No Please describe off-site treatment method (example - biological treatment followed by activated carbon filter): • Discharge to a settling/retention pond: Yes No Please describe: • Discharge to surface water (e.g., river, lake, ocean): Yes No Please describe: • Collection and transfer to an off-site wastewater management facility/company: Yes No Please describe: • Other, e.g. Zero liquid discharge, wastewater for irrigation, evaporation via cooling tower, incineration; deep well injection: Yes No Please describe: Are environmental impacts of API considered in disposal of: • Wastewater? Yes No • Sludge/biomass? Yes No

Audit Overview

Are wastewater discharges or practices in line with the permits issued by local agencies?

Describe how wastewater is managed (dedicated and sufficient staff, documented procedures, condition of facility). If an off-site wastewater treatment plant is used, describe selection/oversight by supplier in Question 50.

Assure that samples are collected, stored, and analyzed with results reported in accordance with local regulatory requirements.

Describe the wastewater treatment flow and treatment methods/treatment technologies used and surface water that receives wastewater effluent from the site. (Include all on-site plant discharges and any off-site treatment plant and the waterbody that receives the discharge).

Describe condition of monitoring equipment and effectiveness of controls. Water/wastewater monitoring devices and treatment systems are in good operating condition and appropriately maintained (e.g., in accordance with manufacturer's recommendations).

Describe best practices used by the site (treatment, capture, and containment or practices especially for highly potent API) to prevent or reduce API discharges in wastewater. Are these controls manually operated or proceduralized?

Describe how APIs are quantified in wastewater: mass balance, sampling with sufficiently sensitive method, etc. Describe risk assessment process and oversight such as procedure available, all APIs accounted for, toxicological info available, competent professional provides oversight, recommendations are incorporated, etc.

Review qualification for persons managing API emissions (i.e. knowledge of regulatory requirements and quantification of APIs in treated waste water)

More on Wastewater Treatment

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

- Treatment volume - Evidence of overspill
- Inspect Final Discharge Point
  - Where does it discharge to-standing waterbody, sewer, river, sea
  - Can you go to see the discharge point
  - What does the effluent look/smell like
    - Strong solvent odour
    - Visible contamination
- Permitted Volumes vs Daily Flows
  - What are they limited to
  - Compliance history
  - Specific parameters
- Treatment Capability
  - Do the know what the treatment type is

More on Wastewater Treatment

Technical Competence

Training/Training Records

Is it operated well

Maintenance and Calibration of Equipment

Routine Inspection

Wastewater Maturity Ladder

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

Minimum

Step 1
Commit & Plan
Basic awareness & knowledge

Step 2
Easy fixes, quick wins, must do's toward prevention and compliance

Advanced

Step 3
Assess Risks

Step 4
Control Risks

High-Level

Step 5
Audit Benchmark

Step 6
Integrate & maintain continuous improvement

40	Indicate which of the following types of air emissions are generated at the facility. Describe the types of pollution control activities if used.	Emission Type	Generated?
		Volatile organic chemicals	Yes No NA
		Corrosive vapors (e.g. acid, caustic)	Yes No NA
		Particulates or dusts	Yes No NA
		Ozone depleting substances	Yes No NA
		Combustion by-products	Yes No NA
		Other Pollutants (e.g., GHG, cyanides, sulfides, ammonias, bromines, phosgene)	Yes No NA

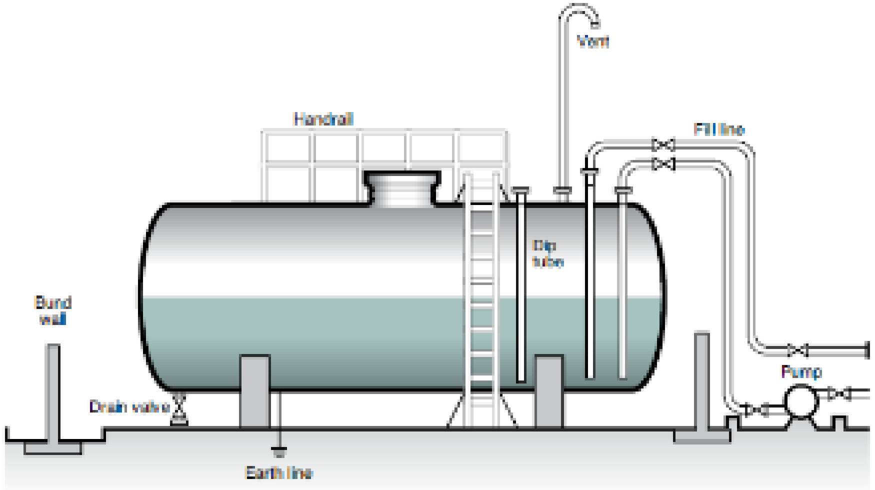
Are the air emissions/air quality monitored periodically as per local regulations?

Are the monitoring reports maintained?
Were there any limit exceedances?

Is the air/emission monitoring carried out internally or a third-party?

Are third-party external labs approved for carrying out the tests?

- Management and control of emissions from storage tanks
- Determine what controls are in place
- Look for controls (and emergency plans) in place for storage of bulk quantities of volatile toxic or highly flammable compounds
- Review Authorisations



More on Air emissions : Process emissions control

- Determine what controls are in place on process equipment
- Determine if the operating parameters and maintenance of the air pollution control equipment is understood and in place
- Review the Authorisation for any specific requirements for vent controls on process equipment

Requirements may include:
•Specific Limits on emissions
•Ambient air quality sampling and limits
•General conditions

More on Air emissions : Odour controls

- Note any odours on your interior and exterior tour
- Review odour control systems in place with facility staff
- Confirm operation and maintenance are adequate to prevent nuisance odours
- Confirm operation is in compliance with the Authorisation

41	Has the facility developed and implemented a hazardous chemicals (including APIs) management program that includes development and maintenance of a current inventory of all hazardous chemicals (including APIs) used, manufactured or stored on-site, including those for production, maintenance, utilities, and laboratory purposes?	Yes No Please explain and list site hazardous substances:

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

42	Has the facility established good storm water management practices?	Yes No Describe how the facility manages storm water and avoid contamination How has the retention volume been calculated? Does it take into account specific factors like rain, environmental hazards of substance stored/handled. Yes No Describe shortly any arrangements that are in place to treat / dispose of the water that would have been collected. Does the facility have a system for controlling and collecting water from fire-fighting to prevent off-site impacts? Yes No Please describe

Is there a dedicated storm water network inside the plant? Describe how the retention volume is calculated and if it takes into account specific factors like rain or environmental hazards of substance stored/handled. Briefly describe any arrangements that are in place to treat / dispose of the water that would have been collected.
If there is no dedicated network, how is storm water collected, measured/analyzed and discharged?

Are there documented programs to manage storm water and storm water contamination control?

Spills and Releases		
43	Does the facility transport any hazardous materials that are subject to a regulatory authority that specifies transportation requirements? (including but not limited to the International Air Transportation Association (IATA), International Civil Aviation Organisation (ICAO), International Maritime Dangerous Goods (IMDG) Code, ADR (formally, the European Agreement concerning the International Carriage of Dangerous Goods by Road (ADR)), U.S. Department of Transportation (DOT).	Yes No Describe how the facility manages the transportation of hazardous materials and dangerous goods

44	Does the facility or immediate surroundings external to the site have any known soil, surface water or groundwater contamination?	Yes No If yes, please provide a brief description of how this is being managed and whether it impacts surroundings of the site (e.g., neighboring facilities, companies), adjacent natural habitats:

Is any soil, surface water or groundwater testing carried out periodically?
Is it required by local regulations?
Are records maintained?

45	Has the facility addressed potential environmental risks arising from storing and handling hazardous substances, including petroleum products and APIs, as follows:	Are there spill containment systems for hazardous substances (including petroleum products and APIs)? Yes No NA Please explain:

Drum storage, above ground tanks, in ground tanks

Secondary containment 110% volume of largest container/tank ?
Leak detection & overfill protection for tanks ?

Spill containment integrity is inspected, documented and maintained in satisfactory condition to prevent the discharge of waste materials into the environment.

Solid wastes are stored, protected from the elements and in a manner to prevent discharge as the result of rain/storm water runoff.

Are waste containers in good condition, compatible with the material being stored and maintained closed except during filling and emptying?

Are protocols or procedures for reporting leaks, spills and other abnormalities related to API waste handling in place and being followed?

Are potential emergency scenarios arising from storage of hazardous substances (including APIs) identified in the site Emergency Response Plan?
Are controls and responses and detailed in the Emergency plan?

Have unpermitted releases been reported to the proper authorities and remedial measures instituted to prevent reoccurrence and address impacts associated with said release?

More on Material Storage Containers & Tanks

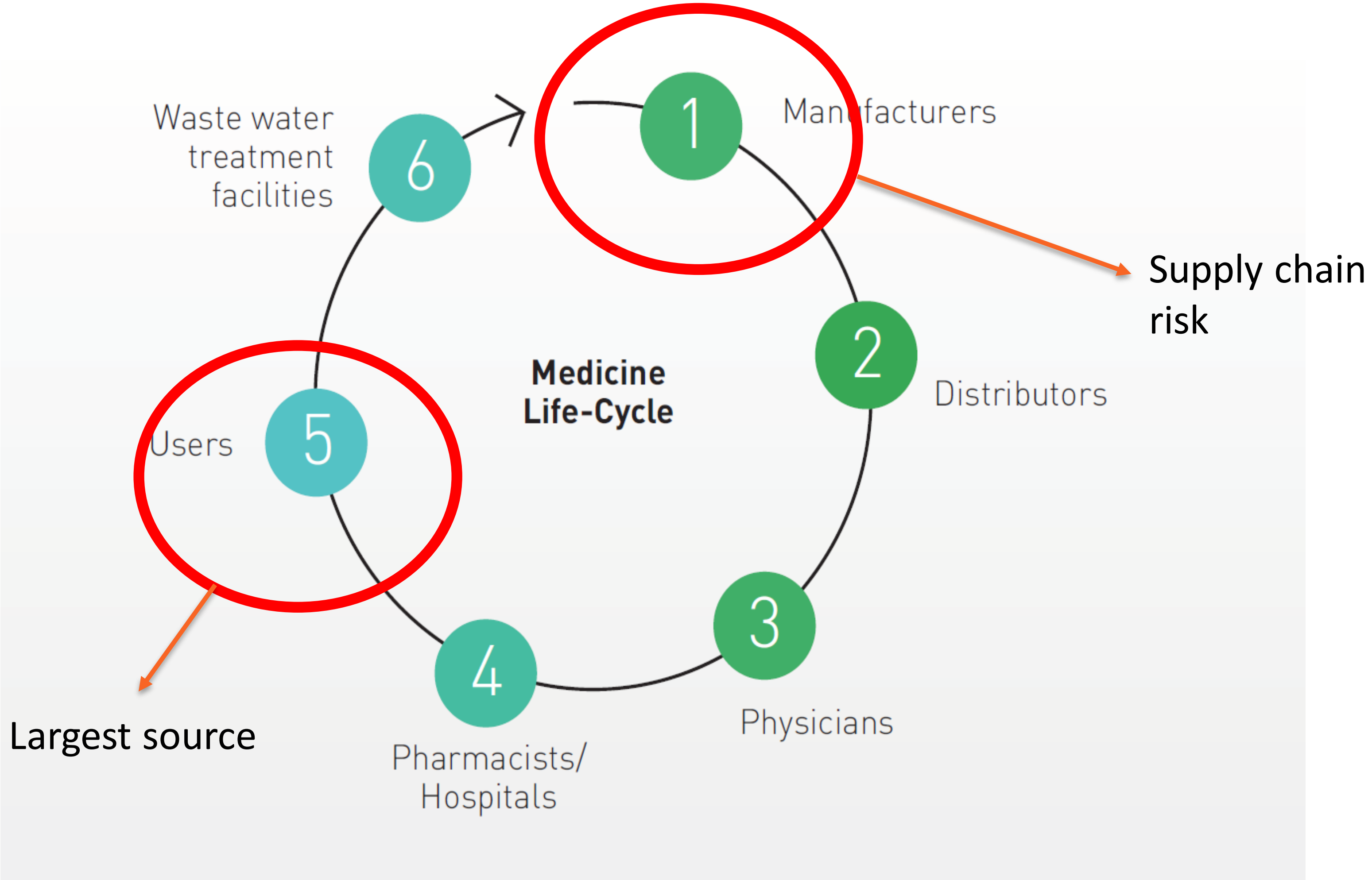
- Review storage of drummed and bagged materials
- Assess if warehouses are properly managed and have containment for potential releases
- Look for poor material storage practices
- Review the requirements of the Authorisation

- Look for appropriate maintenance on tanks
- Do the tanks have overflow and overfill protection?
- Fire detection and suppression
- Check for appropriate containment
- Review tank truck loading and unloading practices

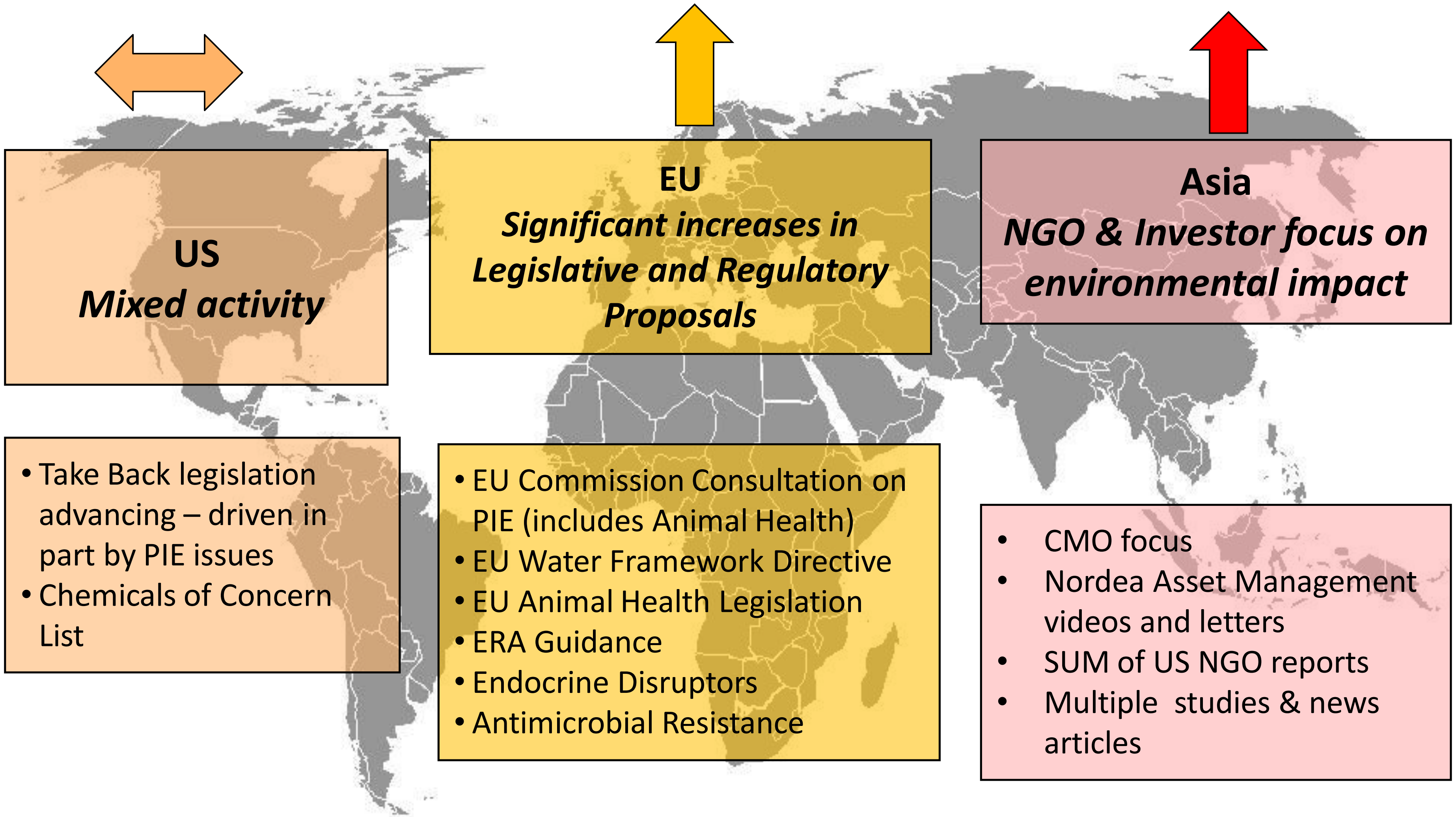
- Where are they?
- Review construction and containment methods
- Review methods used to determine leaks
- Review tank truck loading and unloading practices

46	Are tank truck, railcar, and other bulk transportation unit loading and unloading areas for hazardous substances provided with containment equivalent to at least 110% of the largest transportation unit handled in that area, or for compartmentalized transportation units, equivalent to at least 110% of the single largest compartment?	Yes No NA Please explain:

3. DEEP DIVE
PHARMACEUTICALS IN THE ENVIRONMENT


Waste water treatment facilities
6
1
Manufacturers
Supply chain risk
Medicine Life-Cycle
2
Distributors
Users
5
3
4
Largest source
Physicians
Pharmacists/ Hospitals

Global Perspective



US
Mixed activity

- Take Back legislation advancing – driven in part by PIE issues
- Chemicals of Concern List

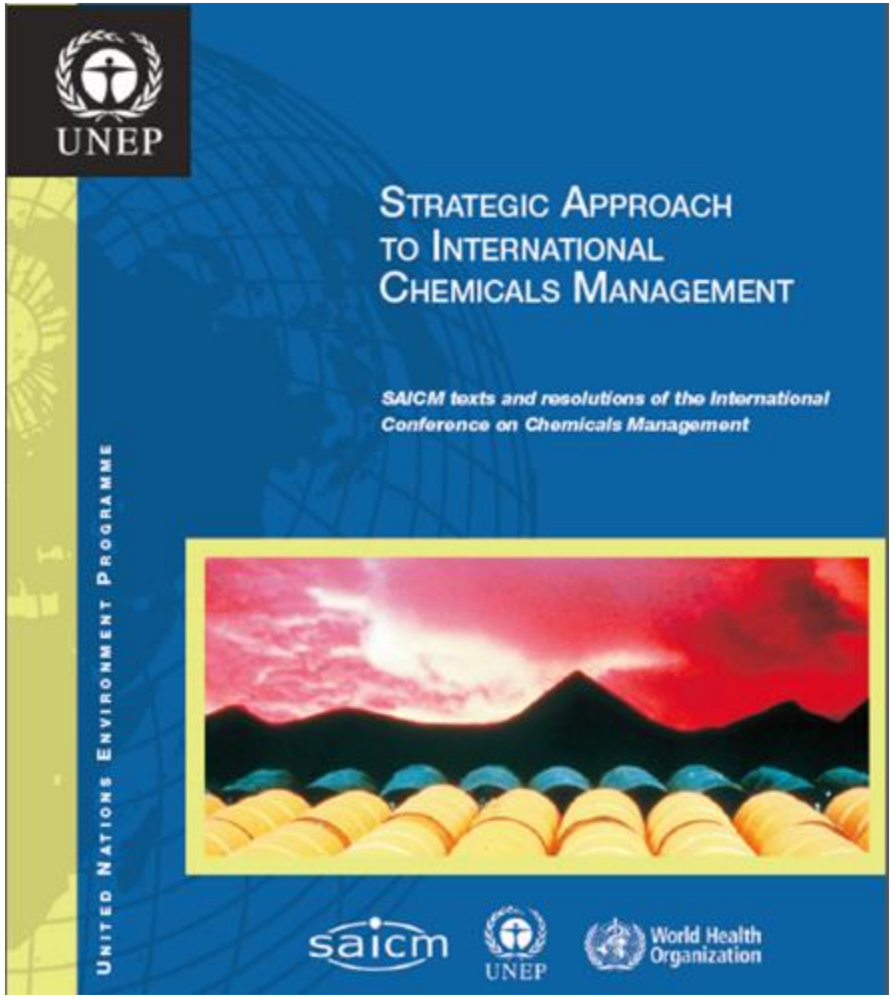
EU
Significant increases in Legislative and Regulatory Proposals

- EU Commission Consultation on PIE (includes Animal Health)
- EU Water Framework Directive
- EU Animal Health Legislation
- ERA Guidance
- Endocrine Disruptors
- Antimicrobial Resistance

Asia
NGO & Investor focus on environmental impact

- CMO focus
- Nordea Asset Management videos and letters
- SUM of US NGO reports
- Multiple studies & news articles

Stakeholders voicing their concerns



At its first session, held in Dubai, United Arab Emirates, from 4 to 6 February 2006, the International Conference on Chemicals Management adopted the Dubai Declaration on International Chemicals Management and the Overarching Policy Strategy. The Conference also recommended the use and further development of the Global Plan of Action as a working tool and guidance document. Together these three documents constitute the Strategic Approach to International Chemicals Management.

Emerging Policy Issues:

- Lead in Paint
- Chemicals in Products
- Endocrine Disrupting Chemicals
- Hazardous substances in electrical and electronic products
- Nanotechnology and manufactured nanomaterials
- Environmentally Persistent Pharmaceutical Products*

*Added October, 2015

Drug Resistance Research

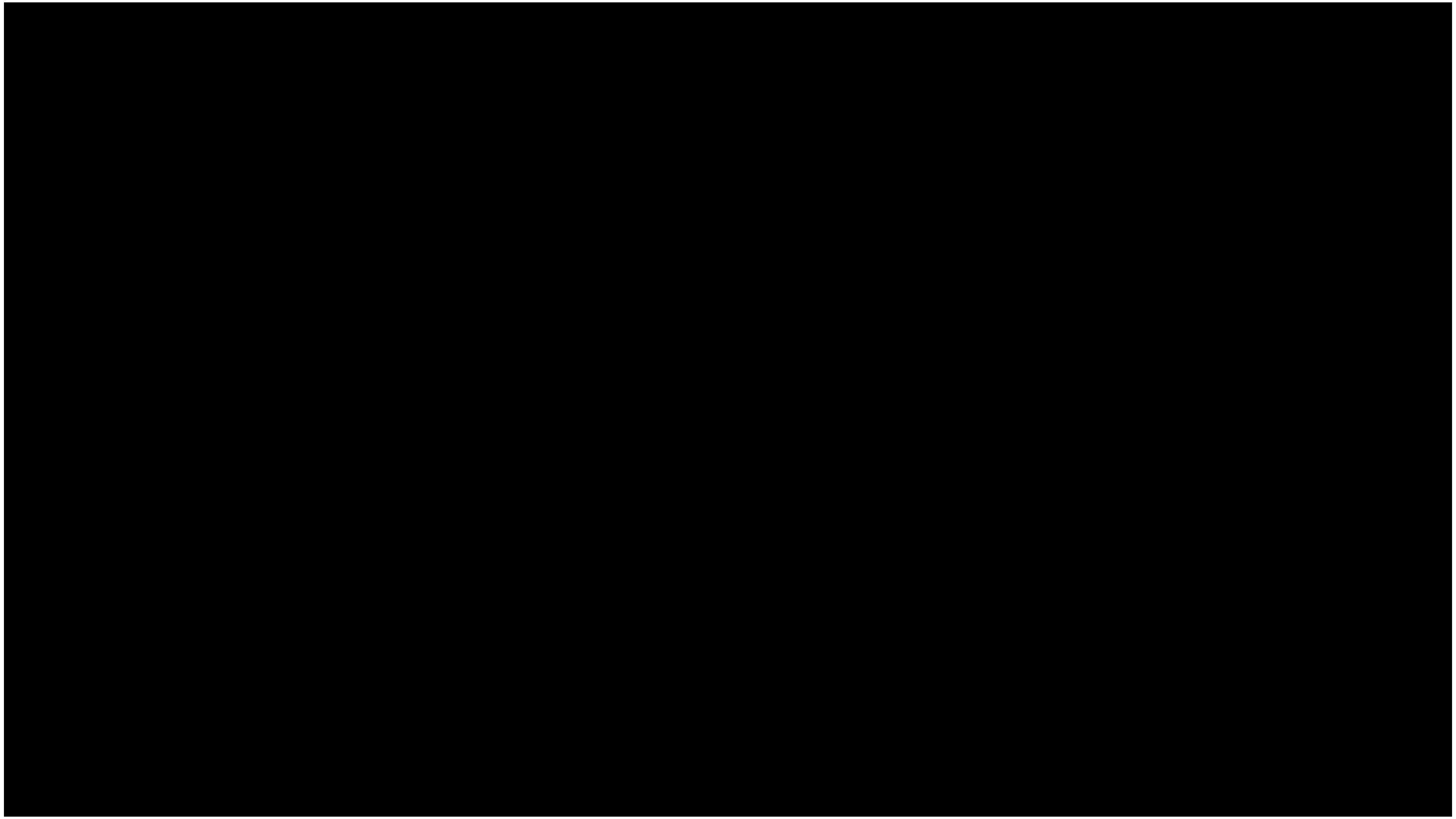
- Harvard Medical School and Technion Institute of Technology demonstrate how bacteria move as they become immune to antibiotics, supported by grants from the NIH and European Health Council*

Courtesy of Harvard Medical School and Technion

- Cinematic Approach to Drug Resistance
- **https://www.youtube.com/watch?feature=player_embedded&v=plVk4NVIUh8**

*A Cinematic Approach to Drug Resistance", Harvard Gazette, September 8, 2016

Drug Resistance Research



Global Response on AMR

- WHO Health Assembly 2015
- UK-One Health Report
- UK- O'Neil Report 2016
- UN General Assembly 2016
- International Federation of Pharmaceutical Manufacturer's and Associations 2016-Davos Declaration

World Health Organization

Reduce Environmental pollution

ESTABLISH MINIMUM STANDARDS TARGETING THE EMISSION OF MANUFACTURING WASTE CONTAINING APIs

ENCOURAGE THE PHARMACEUTICAL INDUSTRY TO DRIVE HIGHER STANDARDS THROUGHOUT THEIR SUPPLY CHAINS

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

O'Neill Final Report - 2016

SIGNATORY COMPANIES

Allergan (NYSE: AGN)
AstraZeneca (NYSE: AZN)
Cipla (NSE: CIPLA)
DSM Sinochem Pharmaceuticals (Euronext: DSM)
F. Hoffman-La Roche Ltd., Switzerland (VTX: ROG)
GSK (NYSE: GSK)
Johnson & Johnson (NYSE: JNJ)
Merck & Co., Inc., Kenilworth, New Jersey, U.S.A. (NYSE: MRK)
Novartis (NYSE: NVS)
Pfizer (NYSE: PFE)
Sanofi (EURONEXT:SAN, NYSE: SNY)
Shionogi & Co., Ltd. (TYO: 4507)
Wockhardt (NSE: WOCKPHARMA)

How we are using PSCI to Address the Issues

- SAQ / Audit tool enhanced with additional API management PIE / AMR questions
- Auditor guidance

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

39	Indicate which methods are used to manage process wastewater from this facility.	Check all that apply to treatment and disposal of wastewater: • Pretreatment of process water Yes No Please describe method(s) (example – hydrolysis with caustic or heat pre-treatment): • On-site wastewater treatment: Yes No Please describe: Does the facility collect, store, and analyze samples? Wastewater? Yes No Sludge? Yes No • Discharge to an offsite treatment facility: Yes No Please describe off-site treatment method (example - biological treatment followed by activated carbon filter): • Discharge to a settling/retention pond: Yes No Please describe: • Discharge to surface water (e.g., river, lake, ocean): Yes No Please describe: • Collection and transfer to an off-site wastewater management facility/company: Yes No Please describe: • Other, e.g. Zero liquid discharge, wastewater for irrigation, evaporation via cooling tower, incineration; deep well injection: Yes No Please describe: Are environmental impacts of API considered in disposal of: • Wastewater? Yes No • Sludge/biomass? Yes No

Audit Overview | New auditor guidance for wastewater

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

Are wastewater discharges or practices in line with the permits issued by local agencies?

Describe how wastewater is managed (dedicated and sufficient staff, documented procedures, condition of facility). If an off-site wastewater treatment plant is used, describe selection/oversight by supplier in Question 50.

Assure that samples are collected, stored, and analyzed with results reported in accordance with local regulatory requirements.

Describe the wastewater treatment flow and treatment methods/treatment technologies used and surface water that receives wastewater effluent from the site. (Include all on-site plant discharges and any off-site treatment plant and the waterbody that receives the discharge).

Describe condition of monitoring equipment and effectiveness of controls. Water/wastewater monitoring devices and treatment systems are in good operating condition and appropriately maintained (e.g., in accordance with manufacturer's recommendations).

Describe best practices used by the site (treatment, capture, and containment or practices especially for highly potent API) to prevent or reduce API discharges in wastewater. Are these controls manually operated or proceduralized?

Describe how APIs are quantified in wastewater: mass balance, sampling with sufficiently sensitive method, etc. Describe risk assessment process and oversight such as procedure available, all APIs accounted for, toxicological info available, competent professional provides oversight, recommendations are incorporated, etc.

Review qualification for persons managing API emissions (i.e. knowledge of regulatory requirements and quantification of APIs in treated waste water)

Pre Assessment Information

- What information can you gather in advance:
  - What APIs do they handle
  - Safety Data Sheets (SDS)-Example
  - Is there any guidance available for the limit to water (PNEC)
  - Where is the nearest water body-receiving water
  - Flow rates of receiving water bodies

API Environmental Risk Assessment

- Good management practices may not eliminate all API released to water
- Site responsibility is to know whether the amount released could have a potential impact on the environment
- Environmental Risk Assessment requires data and professional judgment

Predicted Environmental Concentration **(PEC) (Concentration in Effluent)**

Predicted No Effect Concentration **(PNEC) (Concentration Limit)**

Risk Quotient (RQ)
PEC /PNEC <1, Low risk
PEC /PNEC >1, Potential risk: Reassess/take appropriate action

PEC Data Collection & Analysis

- Review batch records to determine API losses
- Estimate API losses (account for batch and cleaning cycles)
- Estimate treatment plant removal efficiency using the API chemical and physical properties, literature, or assume 0%
- Get wastewater and receiving water flows

Examples

On-Site

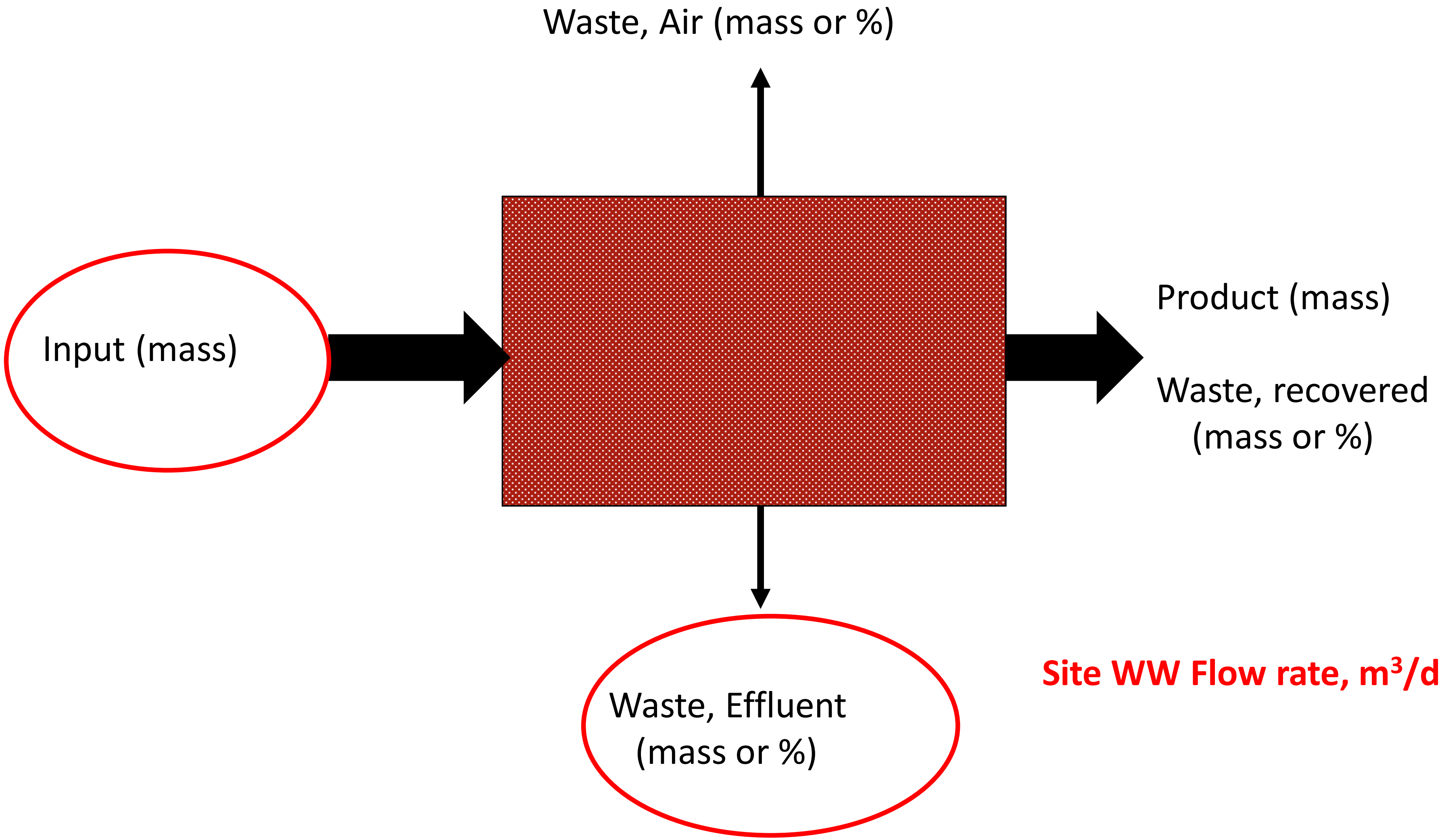
batch records	wastewater POG[1]
product yield	wastewater flows
batch/year	WWTP unit ops
cleaning cycles	API analyses[2]

Off-Site

POTW flow
POTW unit ops
receiving water flow

1 POG = Point of Generation
2 API analysis of wastewater, solvent waste, solid waste, etc.

API Mass Balance



Site WW Flow rate, m^3/d

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Using mass balance values

1. Must be representative of the process
2. Consider control chart for calculated losses

Date of Manufacture	Item Code	# of vials filled	Amount of API in vials (kg), (calculated)	Amount of API not in vials (kg), (calculated)	Daily sum of amount not in vials
04-JAN-2011 14:13:03	000000000000	15767	18.037448	0.095552	0.216272
04-JAN-2011 14:18:08	000000000000	15745	18.01228	0.12072	
11-JAN-2011 14:12:12	000000000000	15740	18.00656	0.12644	0.332416
11-JAN-2011 14:09:54	000000000000	15765	18.03516	0.09784	
11-JAN-2011 14:24:55	000000000000	15756	18.024864	0.108136	
18-JAN-2011 10:52:49	000000000000	15723	17.987112	0.145888	0.283768
18-JAN-2011 10:46:36	000000000000	15730	17.99512	0.13788	
25-JAN-2011 16:24:28	000000000000	15534	17.770896	0.362104	0.491976
25-JAN-2011 16:22:15	000000000000	15737	18.003128	0.129872	
	Avg Number of vials filled	Avg Amount of API in vials (kg)	Avg Amount of API not in vials (kg)	Worst Case API in Wastewater (kg)	Limit API in Wastewater (kg/day)
	15721.89	17.99	0.15	0.29	0.65
				Cumulative Daily Worst Case (kg)	
				0.49	

Calculating the Risk Quotient

$$\text{Risk Quotient (RQ)} = \frac{\text{PEC}}{\text{PNEC}} = <1 \text{ or } >1?$$

Risk Quotient		
Less than (<) 1	Indicates that the expected concentration is lower than the concentration indicating low/no potential environmental risk	
Greater than (>) 1	Indicates that the expected concentration exceeds the no-effect concentration indicating the potential for risk	

Guidance

SETAC PRESS

Environmental Toxicology and Chemistry, Vol. 9999, No. 9999, pp. 1–10, 2015
Published 2015 SETAC
Printed in the USA

Hazard/Risk Assessment

A RISK-BASED APPROACH TO MANAGING ACTIVE PHARMACEUTICAL INGREDIENTS IN MANUFACTURING EFFLUENT

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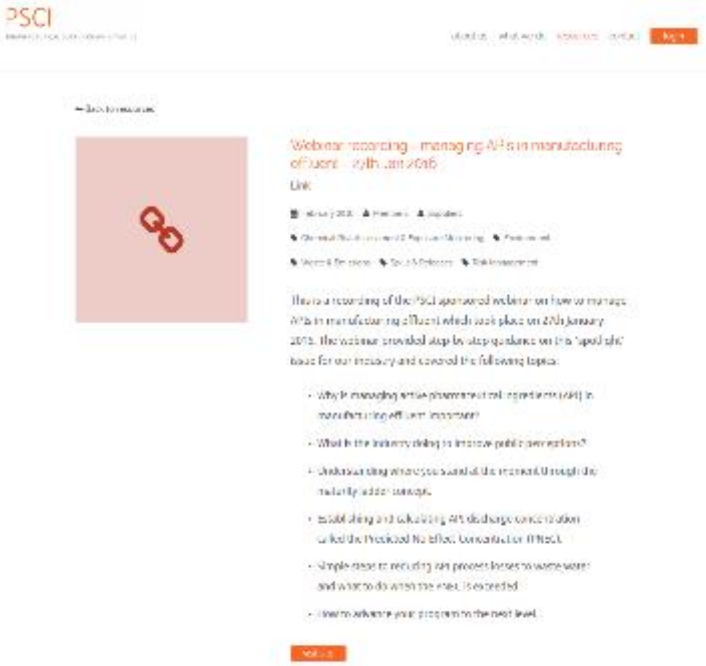

[Caldwell et al Paper](#)

[PNEC Resources](#)

Webinar series:

[Part 1](#)

[Part 2](#)

[Part 3](#)

[Part 4](#)

Permits

We are complying with our Permit

- Most discharge permits will address established parameters, e.g., control of pH, biological oxygen demand, chemical oxygen demand, etc.
- Some discharge permits include periodic general toxicity testing, i.e., whole effluent toxicity
- Most discharge permits will <u>NOT</u> directly address active pharmaceutical ingredients (APIs) but <u>DO</u> include a ‘general duty’ clause, i.e., “No toxics in toxic amounts”.

Type of mitigation strategy depends on local specs :

- Waste water flow on site/WWTP configutation
- Type & number of 'problematic' APIs

At source mitigation

- Targeted waste stream with highest API load
- Single API mitigation
- GMP consideration (inside plant)
- $

Pre-treatment

- Treat multiple waste streams, multiple API mitigation
- Avoid full flow of Waste Water treatment
- No GMP (outside plant)
- $$

End of pipe treatment

- 'Polishing' step after WWTP
- 'All inclusive'
- No GMP (outside plant)
- $$$

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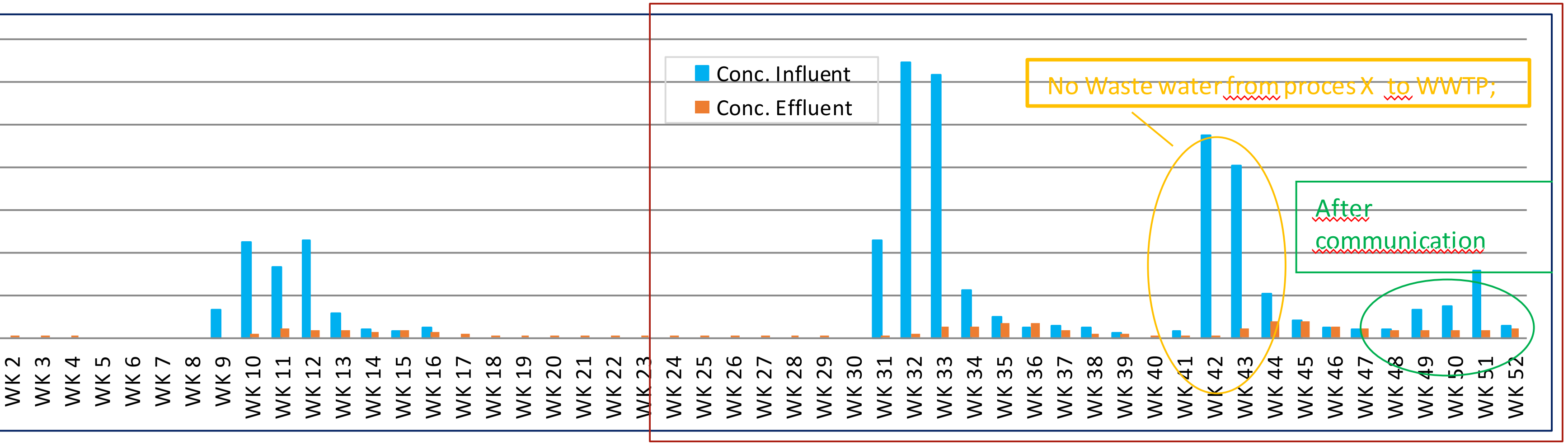
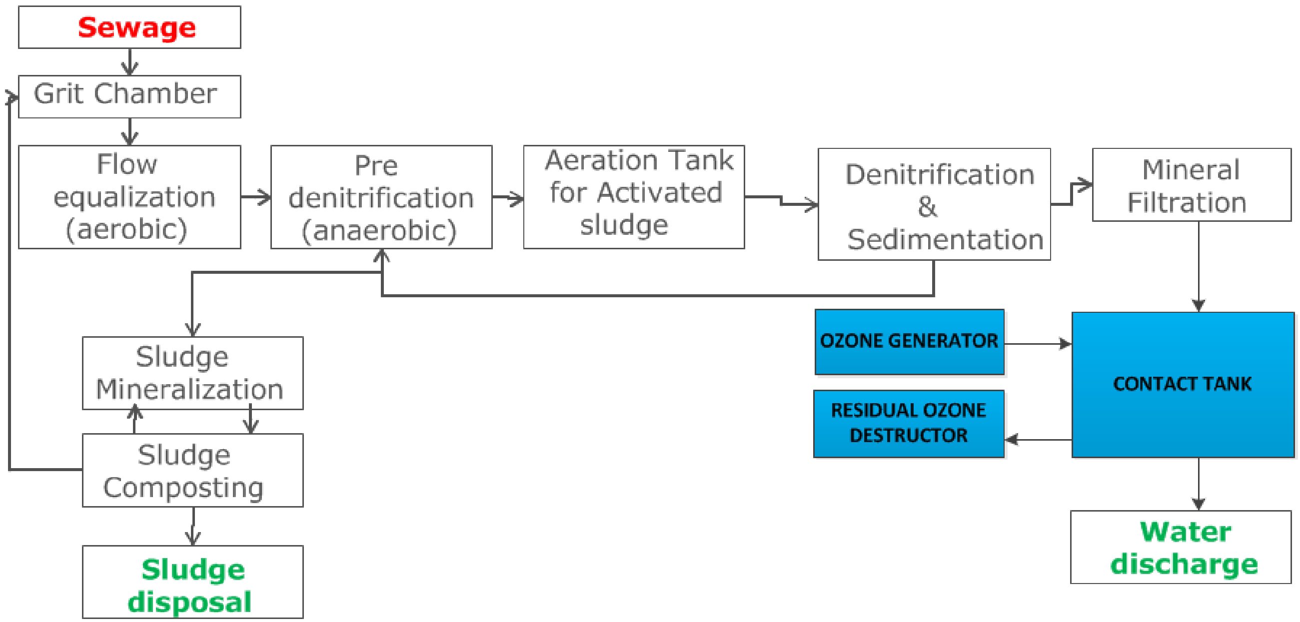
- At source mitigation @ API chemcial manufacturing plant
  - Discard process wastewater with ‘problematic compound X’ to incineration instead of WWTP
  - Investigation with procesmanager → during emptying of centrifuge, some product falls on floor and is flushed to sewer → include good practice in SOP to avoid flushing residual powders in sewer



PIE mitigation | Examples

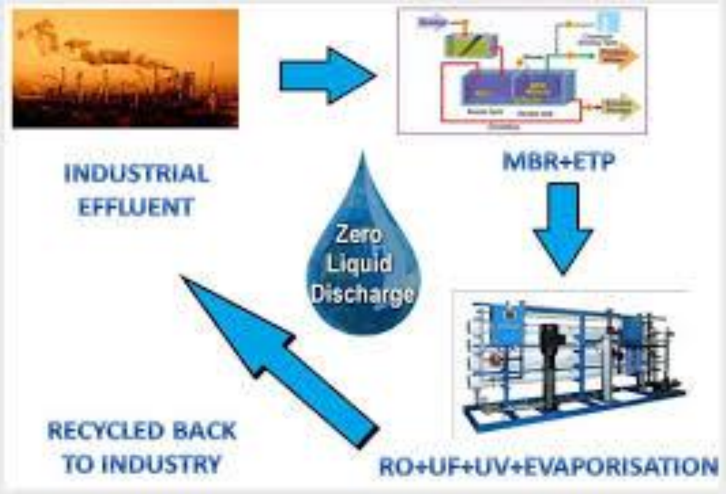
- Pre treatment @ API chemcial manufacturing plant : mobile equipment to treat process streams
  - Remove API from production wastewaters with modular technology (advanced oxidation/adsorption/etc.)
  - Pre-treated water can furter be treated in on site water treatment plant
  - Equipment can be trucked to other locations (other plants e.g.)

- End of pipe MBR + ozone treatment @ fill&finish Pharma plant



Zero Liquid Discharge

- Zero Discharge-Reuse of treated effluent
- Check the mass balance volumes-
  - e.g. is the daily amount of effluent the same as the input to the cooling towers
  - is the volume far greater than irrigation use
- ZLD Doesn't always equal 'zero risk'. Ground dispersion may result in:
  - Dermal/inhalation exposure to applicator and/or recreational users
  - Edible vegetation and/or groundwater users
  - Terrestrial organisms
  - Mist inhalation from opened cooling uses



PIE Case Studies

PIE/AMR CASE EXAMPLE for Company A On-site Treatment Removal Performance of API

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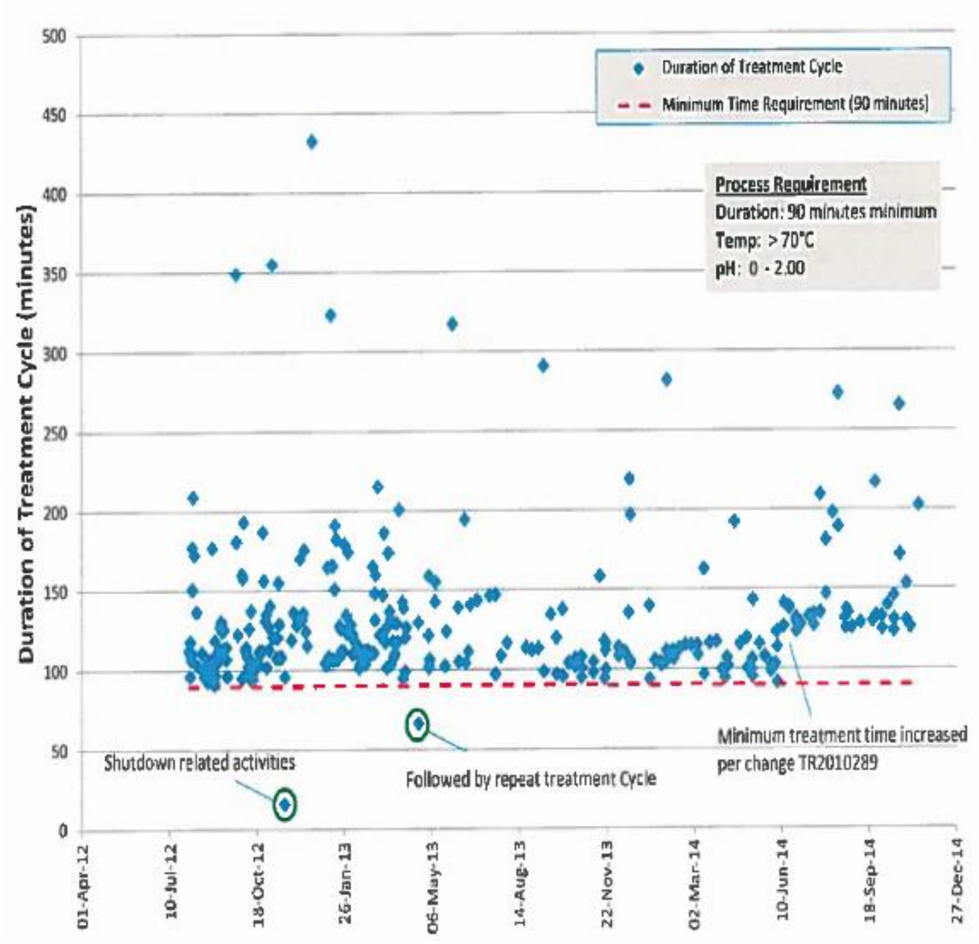
- Batch wastewater Fill/Finish API collection and treatment system
- Performance testing of acid plus high temperature treatment showed 95% API destruction
- Process requirements
  - Temperature >70°C
  - pH 0 – 2.00 s.u.
  - ≥ 90 minutes



EXAMPLE Audit Questions to Consider:

1. Is appropriate staffing provided to manage and implement programs to control emissions of active ingredients?
2. What are the business area’s written qualifications for persons performing and reviewing environmental calculations.
3. How were the process requirements for temperature plus time and pH determined? How does the site ensure that the wastewater content has not changed to impact treatability?
4. Is the treatment system manually operated systems
5. Are other physical barriers (plugged floor drains) in place and do all API containing wastewaters go to this treatment system?
6. Are appropriate systems in place to control the loss of active ingredient to wastewater from production (i.e. to ensure we do not have treatment breakthrough)?

PIE/AMR CASE EXAMPLE for Company A Off-site Treatment Removal Estimates

Example API removal through a municipal Conventional Activated Sludge (CAS) system with a biodegradation half life of 7.2 hours and a 6 hour CAS Hydraulic Retention Time (HRT)

Basic Calculation Method

To solve for the effluent concentration for the biological treatment plant with an influent concentration of 200 ug/L API after biodegradation assuming a 6 hour biological treatment plant retention time and a compound half-life of 7.2 hours, we can use the following equations:

Determination of k (biodegradation rate per hour): $\ln 2/1\ k\ t_{½}$ → $0.693 = k(7.2\ \text{hrs.})$ → $k = 0.096\ \text{hrs.}^{-}$

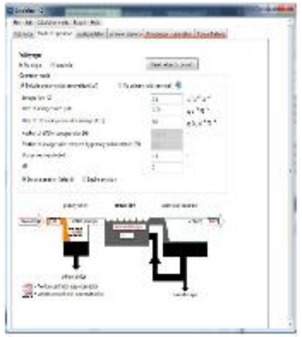
Determination of At (final effluent concentration after biodegradation) is calculated as follows:

$\ln[200\ \text{ug/L influent}]/[At] = (0.096\ \text{hrs.}^{-})(6\ \text{hrs.})$ → $200\ \text{ug/L} = [At]\ e^{(0.096\ \text{hrs.}^{-})(6\ \text{hrs.})}$ → $200\ \text{ug/L} = [At]\ e^{0.576}$ → $200\ \text{ug/L} = [At]\ 1.779$ → $112.42\ \text{ug/L} = At$

Municipal % Removal = [1 - (112.42 ug/L/ 200 ug/L)] X 100 = 43.8%

Modeling Methods

SimpleTreat (available at: https://www.rivm.nl/en/Topics/S/Soil_and_water/SimpleTreat

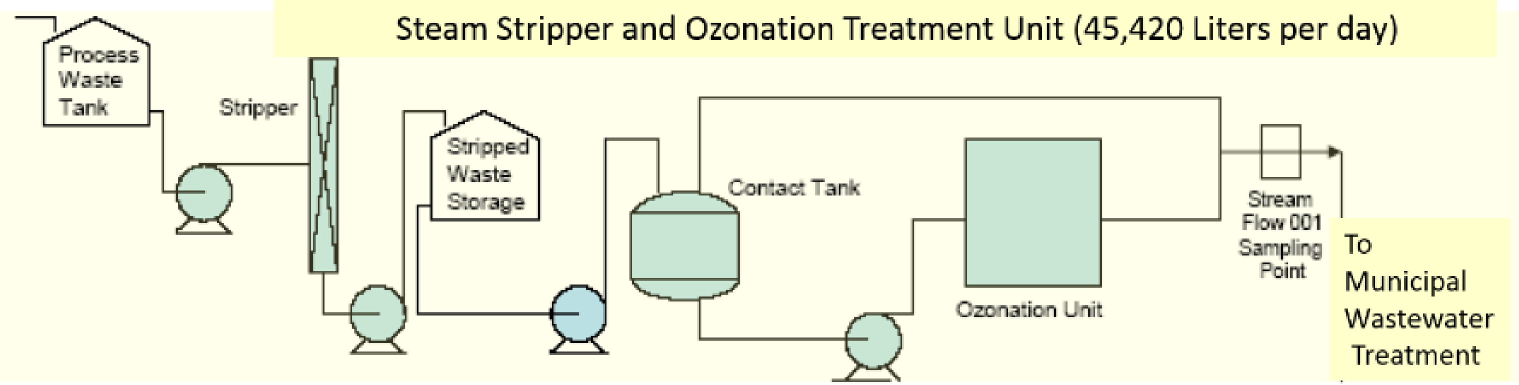


EXAMPLE Audit Questions/Actions to Consider:

1. Was the credit for biological treatment evaluated by a qualified person?
2. Are references or studies available to verify the assumptions that went into modeling the removal credit?
3. What are the critical process variables (HRT, MLSS, BO or COD removal rates, etc.) for the CAS system used to ensure that it routinely achieves the calculated API removal credit
4. If the site uses a model like SimpleTreat verify that the assumptions used for modeling were appropriate and representative.

PIE/AMR CASE EXAMPLE for Company B
On-site Treatment and Control of API Discharge

- 2 Bulk chemically synthesized APIs manufactured at this site
  - Product A – All waste streams collected for off-site incineration -system cannot physically discharge to the wastewater sewer system
  - Product B - Batch Wastewater Collection and Treatment System



EXAMPLE Audit Questions/Actions to Consider:

For Product A
1. Field verify that system is not physically connected to the sewer system
2. Verify that wastewater is sent to an incineration system

For Product B
1. Review the treatment design studies to verify the assumptions that went into designing the treatment system
2. What are the critical process variables for the ozonation system used to ensure that it routinely achieves API removal credit
3. Verify that the assumptions used for using the municipal treatment system are adequate (i.e. size, treatment provided, location of discharge)

4. EXAMPLE AUDIT FINDINGS

- Paint a picture for reviewers in the report as if they have never been to the site
- Be specific where possible to provide context of scope of issue, impact to supply chain, depth of problem
- Accurate without overstating or understating issue

Q39: Indicate which methods are used to manage process wastewater from this facility.

Real PSCI audit finding

The site has no evidence about the effectiveness of the private waste water treatment works.

What kinds of wastes are sent to the private waste water treatment works?
Is the site required to use this private waste water treatment works?
Does the site characterize waste water sent offsite?

Case 1 – Model finding

The site sends production wastewater to a private wastewater treatment plant via hired tanker truck daily.

The private wastewater treatment plant is the common local plant the site (and rest of industrial park) is required to use. The site characterizes the wastewater going offsite so quantity of API in discharge is known. The site has requested/been refused/not yet received information on treatment capability and effectiveness of the private wastewater treatment plant.

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Q45: Has the facility addressed potential environmental risks arising from storing and handling hazardous substances, including petroleum products as APIs, as follows: …
Does the site have protocols or procedures for storing and handling drums, providing containment for drums and managing spills from drums?

Real PSCI audit finding

Some hazardous wastes (empty chemical containers) stored in the open air.

Quantity?

Size?

On concrete pad, on soil, etc?

Case 2 – Model finding

Approximately 40 empty 55 gallon metal drums (previously containing hazardous chemicals) were stored on loading dock of Building 16 with no protection from the elements.

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Q45: Has the facility addressed potential environmental risks arising from storing and handling hazardous substances, including petroleum products as APIs, as follows: … Does the site utilize Secondary containment in the form of double walled tank and piping or an external vault with a capacity equivalent to 110% of the largest tank or vessel in the containment area?

Real PSCI audit finding

Containment at tank farm is not adequate.

What kind of containment – double wall, vault…

What is the deficiency? Too small, breach, not compatible with material stored, doesn't exist…

How would you improve this finding?

Instructions

1. Use the audit finding sheet provided to write up the finding.
2. **Add details from your experience** not mentioned in the bad finding example.
3. You have 5 minutes (or less time if everyone is finished)
4. Afterwards we will discuss your answers

Exercise 1 - Sample finding

Tank farm storing solvents has concrete pad and berm surrounding tanks but 3 breaches have been cut into concrete to accommodate rain water removal, compromising the integrity of the berm.

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Practice writing audit finding:

Write an audit finding based on the below gathered information:

- These drums were stored at the backyard of a site that manufactures API intermediates
- 3 out of 5 drums were empty, 2 were half-full (content unknown, strong odor of organic solvents noticed)
- The site also handles hazardous materials

Exercise 2 - Sample finding

Behind the waste storage building, 5 rusty drums were stored directly on the soil without any further labeling or protection against the environment.

Three out of five drums were empty, two were half-full with an unknown content, a strong odor of organic solvents was noticed.

Furthermore other trash including other glass pieces, plastic boxes as well as cleaning equipment was found nearby these drums.

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PSCI Auditor Training 2018
Audit Report Writing

Doreen Parrish

DOREEN PARISH

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

Head of EHS Systems & Continuous Improvement,

Global Environment, Health & Safety - Shire

- 28 years working in pharma
- (previously Abbott, Hospira, Amgen, Novartis)
- Previously R&D chemist, chemical purchasing, medical device product & project manager , hazardous waste operations
- BS in Organic Chemistry
- Volunteers for in-need organizations

AGENDA

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1. Perception and instructions
2. Principles of good audit findings
3. What's wrong with these audit findings?
4. Classification of audit findings
5. Exercise: write audit findings

An exercise in Expertise

"I speak English"

- Who can watch TV in English?
- Who knows 100+ words in English?
- Who can make a technical presentation in English?
- Who considers themselves fluent in English?
- Who's "mother tongue" is English?
- Who is an expert (degree or certified) in English grammar?

Even the "experts" may not be true experts. We need each other and of course Google!!

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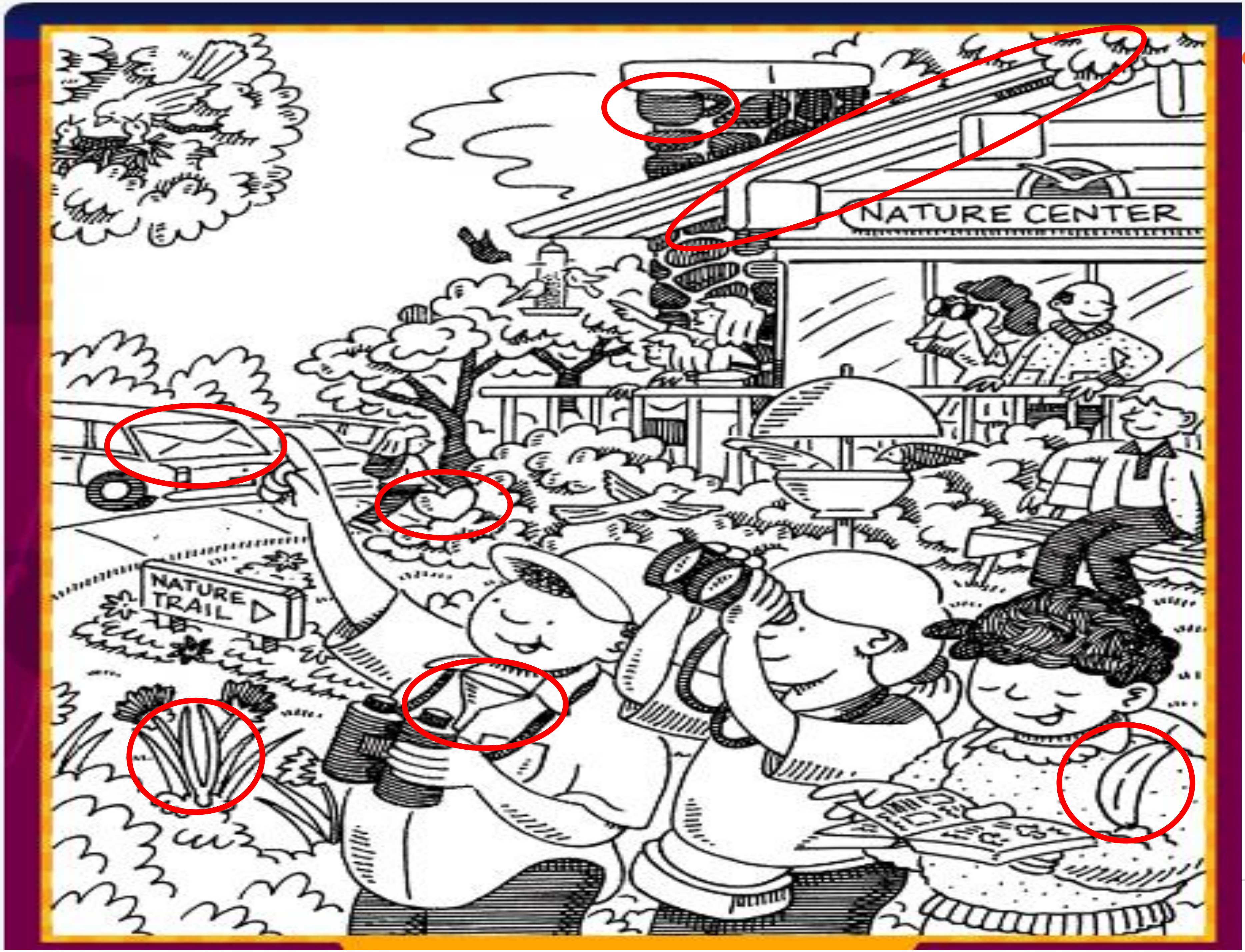
Which lady do you see?



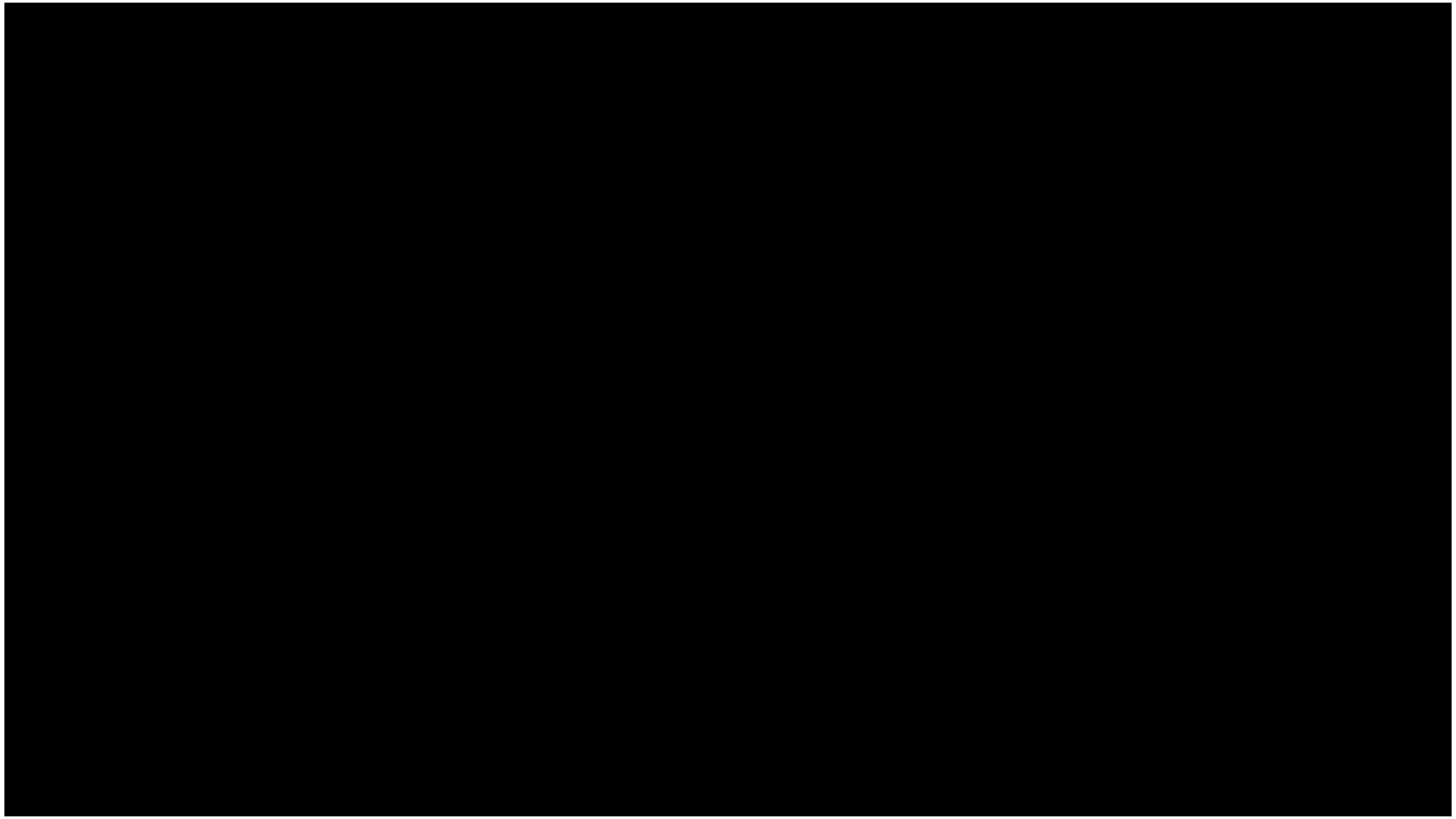
- 杯子
- 信封
- 镊子
- 曲棍球棒
- 漏斗
- 香蕉
- 心

- Coupe
- Enveloppe
- Pince à épiler
- Crosse de hockey
- Entonnoir
- Banane
- Cœur

- Tasse
- Briefumschlag
- Pinzette
- Ice Hockeyschläger
- Trichter
- Banane
- Herz

- Cup
- Envelope
- Tweezers
- Hockey Stick
- Funnel
- Banana
- Heart

1 - INATTENTION BLINDNESS



Inattentional blindness, also known as **perceptual blindness**, an individual fails to recognize an unexpected stimulus that is in plain sight.

Cognitive capture or *cognitive tunneling*, is an inattentional blindness phenomenon in which the observer is too focused on instrumentation, task at hand, internal thought, etc. and not on the present environment. For example, while driving, a driver focused on the speedometer and not on the road.

An exercise in perception and asking questions in communication

- I will give you verbal instructions.
- You must follow these instructions as given.
- You must follow these quietly.
- You are not allowed to ask any questions.
- You should not get help from others around you.
- You should not look at other people's work

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Meaningful Instructions & Feedback:
Essential in our business and during audits

- Did you end up with similar patterns or everyone's pattern was different?
- Why is that?
- Were the instructions clear enough?
- Was something missing?
- Why is feedback so critical in communication?
- What happens if feedback is missing?
- What lessons do we take from this?

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Audit findings are a particularly challenging form of writing. They

- usually involve **technical points** describing a **discrepancy from requirements**
- must accurately communicate **factual information**
- must be in an **unambiguous language** to state - as **simply as possible** - what was found.
- should be **understandable to any reader**. Specifically, they must **be clearly understood by the supplier** responsible for corrective actions.

2 – WRITING AUDIT FINDINGS

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Following basic questions should be considered while writing a finding:

- **Who?** is involved in the finding
- **What?** is the subject of the finding
- **When?** did the finding take place
- **Where?** was the location of the finding
- **How?** did the finding come about and examples
- **How often?** does the finding happen: a single event/case or a systematic error

And: Challenge significance of each observation by asking "So what?"

Write facts

Base your audit report entirely on the **evidence** you have gathered. **Avoid** any statement of **opinion**.

Examples

Opinionated statement	*Replaced with factual statement*
The facility's contingency plan is **inadequate**.	The facility's contingency plan lacked the following elements: agreement with local authorities, types and locations of fire protection equipment and up-to-date listing of emergency telephone numbers

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Use evidence

Be **specific** in the evidence that you present. Consider whether you have answered key questions such as **when, where, how many, by whom** and **how** and, if you have not, add further detail. Provide **context**.

Too general

- Emergency exit signs are missing.
- Three fire extinguishers at the site did not have the required inspection tags.

Improved by adding precise details

- Two emergency exit signs were missing in the following areas:
  - in an unused warehouse and
  - in the QC laboratory (room No 512)
- The team inspected 10 of 80 fire extinguishers at the site. Three fire extinguishers in the QC laboratory did not have inspection tags.

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Avoid extreme language and speculations

Refrain from using words like **dangerous, severe, terrible** etc. as they are not helpful in communicating of the exact nature of the problem.

Extreme language

- The lack of documented confined space entry procedures for the manufacturing operations may lead to dangerous situations.

Better wording

- Confined space entry procedures were not available in manufacturing.

Speculation

- The site does not have a secondary containment for Nitric acid. Any releases would spill onto soil and enter the groundwater.

Just the fact

- Two of 111 100 liter drums of Nitric acid were observed to be stored in room 234 without secondary containment.

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Only factual conclusions

Provide statement of requirements (e.g. legal reference) where possible but **do not draw legal conclusions**.

Legal conclusion

- The company does not have a Fire safety authorization in place (No-Objection Certificate), this is not in compliance with the Shanghai State Fire Services Act 1999.

Factual conclusion

- A Fire safety authorization was not available. Citation - As per the Shanghai State Fire Services Act 1999 a Fire safety authorization (No-Objection Certificate) is required.

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No overstatement of conclusions

Clearly state the nature of the problem; **do not overstate conclusions**

Too general

- Instruments are not being calibrated.

Overstated conclusion

- The facility has no respiratory protection program.

More detailed and exact information

- The sampling and analytical instruments in the wastewater treatment plant were not part of the calibration program.

Exact observation

- The facility’s respiratory protection program did not include fit testing, routine inspection and maintenance of respirators.

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Avoid relying on hearsay evidence alone

Statement based on Hearsay

- An operator mentioned that 2 fatalities occurred in Production Block H during 2016.

Statement based on evidence

- The Incident investigation report no. xxx dated xx.xx.2016 indicated that 2 fatalities occurred due to a fire in Production Block H.

Avoid indirect expressions

Statement using the word 'Appear'

- It appears that the air monitoring equipment is not calibrated.

Statement mentioning what was observed

- Annual calibration data / reports was not available for air monitoring equipment for years 2016-2018.

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No criticism of individuals or their mistakes

Do **not criticize individuals** or highlight their mistakes in an audit report. **Ensure privacy** of individuals is maintained. **Never use unique identifiers** in audit reports e.g. names, Company ID numbers.

Pinpointing individuals

- Mr. Jing and Mr. Xu were observed ……

Improved by removing the names of individuals

- The team observed two maintenance personnel……

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Avoid Abbreviations

Not all recipients of the report will be involved in health, safety and environmental activities on a daily basis and, thus, they may not be as familiar with the health, safety and environmental acronyms, abbreviations, and regulatory jargon as the auditors are.

Using abbreviations

- There is no evidence showing that the facility measures TSS, BOD, and oil and grease in its discharges to the CETP.

Improved by including full forms

- Monitoring records for discharges to the common effluent treatment plant (CETP) were not available. It was indicated the facility measured total suspended solids (TSS), biochemical oxygen demand (BOD), and oil and grease.

2 – SUMMARY

- **Do not wait until the audit is over to start thinking about writing the report!**
- **Gather all details** and investigate links when possible.
- Answer basic questions: **Who ? What?, When?, Where?, How?, How many** and **So what? (Context)**
- Build on findings by asking **"Why?"** for possible root causes.
- Keep the written observations **simple, clear, objective, and factual.**
- Write in the **past tense**. Everything that was observed is now in the past. Writing in the present means things are still occurring but audits are snap shots in time.

3 – WHAT´S WRONG WITH THESE AUDIT FINDINGS?

FINDINGS	MISTAKES
There was minimal on-site compliance with Corporate or department contractor safety policy and procedures.	
Some of the air sources were being operated without proper permits and some are not adequately maintained.	
The facility's central MSDS file was very neat and accessible to those employees who should see it. Not all materials used or stored by the facility have MSDSs in the central file. Those MSDSs reviewed appeared complete and contained the appropriate information.	
Bob Miller was neither familiar with the company's SOP on Hazardous materials nor could he identify where MSDSs were located.	

3 – WHAT´S WRONG WITH THESE AUDIT FINDINGS?

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FINDINGS	MISTAKES
There was minimal on-site compliance with Corporate or department contractor safety policy and procedures.	Not specific. Does not describe the problem in detail so that the factory can correct it.
Some of the air sources were being operated without proper permits and some are not adequately maintained.	
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Building responsible supply chains

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There was minimal on-site compliance with Corporate or department contractor safety policy and procedures.	Not specific. Does not describe the problem in detail so that the factory can correct it.
Some of the air sources were being operated without proper permits and some are not adequately maintained.	Do not use words like some, proper or adequately. Which sources? How many?
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The facility's central MSDS file was very neat and accessible to those employees who should see it. Not all materials used or stored by the facility have MSDSs in the central file. Those MSDSs reviewed appeared complete and contained the appropriate information.	What does MSDS mean? Audit findings and good observations are combined here. Do not use words like "not all" and "appears".
Bob Miller was neither familiar with the company's SOP on Hazardous materials nor could he identify where MSDSs were located.	

3 – WHAT´S WRONG WITH THESE AUDIT FINDINGS?

FINDINGS	**MISTAKES**
There was minimal on-site compliance with Corporate or department contractor safety policy and procedures.	Not specific. Does not describe the problem in detail so that the factory can correct it.
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Bob Miller was neither familiar with the company's SOP on Hazardous materials nor could he identify where MSDSs were located.	Avoid using names and personal accusations.

FINDINGS	MISTAKES
The audit team was told that there have been a number of spills of hazardous materials by the maintenance staff. The audit team recommends that these individuals be disciplined and retrained.	
It seemed that the emergency routes in the warehouse were too narrow.	
An operator reported work permits were not always issued when staff enter confined spaces. This violates the site´s confined space entry program.	
The chemical hygiene plan was found deficient and should be improved. This is a serious concern.	

3 – WHAT´S WRONG WITH THESE AUDIT FINDINGS?

FINDINGS	MISTAKES
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It seemed that the emergency routes in the warehouse were too narrow.	
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The chemical hygiene plan was found deficient and should be improved. This is a serious concern.	“Deficient” sounds opinionated; “serious” – avoid extreme wording

Critical Findings:

- Are **very high risk findings** that require immediate action to protect human life, the health of employees or the environment;
- May **result in loss of license to operate or serious damage to reputation**;
- Require **immediate corrective action** by the supplier;
- **Need to be communicated to PSCI member or PSCI secretariat prior to audit report finalization.**

Examples for Critical Findings:

- Operation of a solvent storage facility without legally required permit
- Intentional shut-down or bypassing of important safety installations

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Other Findings:

- Are all other **major or minor** audit findings which need to be corrected in an appropriate period of time

Examples of Other Findings:

- Inspection of portable fire extinguishers not carried out monthly
- Not all safety data sheets are available in local language
- Hazard communication labeling missing on some bottles and drums
- *Facilities respirator protection program lacks fit testing*
- Safety training missing in a some cases and for some topics

All findings need to be summarized in the PSCI Corrective Action Plan


CRITICAL
CRITICAL
MAJOR
Minor

Are these critical, other (major) or other (minor)?

- The Streba 30 Fluid Bed Granulator used for substances (containing micronized active pharmaceutical ingredients) with dust explosion properties was run without any pressure relief device (pressure relief flaps had been set out of function). During the audit, the pressure relief flaps were set into operation again, but the proper function in case of dust explosion is not ensured. The pressure relief is directed into the working room.

  CRITICAL

- The natural gas pipe from the gas transfer station to the boiler house was not identified / labeled

  OTHER (MINOR)

- Eight 100 l drums containing used organic solvents – waiting for distillation – wer stored in the outside distillation area without any retention basin and next to the rainwater drainage which runs to the river.

  OTHER (MAJOR)

Are these critical, other (major) or other (minor)?

- The safety data sheets for the cleaning agents 1273 and 1322 used in the production area were only available in English and not in the local language.

  OTHER (MINOR)

- 4 out of 5 emergency exit doors in the raw material warehouse and 4 out of 7 emergency exit doors in the canteen were found locked by padlocks.

  CRITICAL

- Eye showers and/or eye wash bottles were not available in the following areas where corrosive liquids are handled: Cleaning room of Quality Control Laboratories and Microbiological Laboratory (corrosive cleaning liquids), cleaning room of non-hormonal production building A100 (corrosive cleaning liquid) Battery charging rooms in warehouse A, B and C (acids)

  OTHER (MAJOR)

Write an audit finding based on the information below :

- Site manufactures intermediates and active ingredients
- The water seen in the picture is the outcome from the washings of the empty reaction vessels and reaction room
- This is the general practice at the facility
- This was repeatedly observed also in follow-up audit

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Possible solution

- Discharge water observed coming from the cleaning of the reaction vessels and the reaction rooms used for the production of intermediates and active ingredients was discharging directly onto the ground/soil around the site without treatment.
- This was a repeated observation / finding during the initial audit. (but no corrective actions have been implemented so far.)

Further points to consider: waste water procedure at the site, batch records, CAPA system (corrective & preventive actions)…

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PSCI Auditor Training 2018
Day 2

Vienna, 4 – 5 December 2018

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Occupational Health and Industrial Hygiene

PSCI IH Capability Building Team

DOREEN PARISH

- 28 years working in pharma
- (Currently Shire, previously Abbott, Hospira, Amgen, Novartis)
- Previously R&D chemist, chemical purchasing, medical device product & project manager , hazardous waste operations
- BS in Organic Chemistry
- Volunteers for in-need organizations

Benoit BARUTEAU

PSCI Role: Audit Committee member

Company Job Title: HSE Audit API Suppliers

- Engineering and production manager in a pharmaceutical plan
- HSE manager at site level then at HSE sanofi corporate
- HSE Coordinator for R&D sites, Supply Chain Activities, Pharma Injectables Platform, ….

TRAINING STRUCTURE

1. **Audit overview – 10 mins**
2. **Subject overview –20 mins**
3. **Problem topics – 30 mins**
4. **Example audit findings – 45 mins**
5. **Audience questions – 10 mins**

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Audit Questions Summary – Occupational Health and Industrial Hygiene

Topic	Question summary
Occupational Health and Industrial Hygiene	• Risk assessments for chemicals handled? • Occupational exposure level (OEL) values for APIs and hazardous substances • Exposure control capabilities for pharmaceutical compounds • Lowest control range of containment for dust/powder handling • Risk-based medical monitoring or employee health surveillance • Plan to protect First Aid Responders and Medical Professionals from body fluids • Exposure monitoring for the following health and safety risks • Site procedure to inform employees of the results of exposure evaluations and monitoring • Personal Protective Equipment (PPE) for face, eye, foot, head, body and hand protection • Respiratory protective devices and/or engineering controls • Respiratory protection equipment • Fit testing, training, use, cleaning, inspecting, storing, and maintenance of respirators
Hazard Information	• Safety Data Sheets (SDSs) for all hazardous substances

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What are the PSCI Health & Safety Principles applicable to IH?

1. Worker Protection
Suppliers shall protect workers from over exposure to chemical, biological, physical hazards and physically demanding tasks in the work place and in any company provided living quarters.

3. Emergency Preparedness and Response
Suppliers shall identify and assess emergency situations in the workplace and any company provided living quarters, and to minimize their impact by implementing emergency plans and response procedures.

4. Hazard Information
Safety information relating to hazardous materials - including pharmaceutical compounds and pharmaceutical intermediate materials - shall be available to educate, train, and protect workers from hazards.

- Don’t just answer yes/no
- Identify what they do and let the PSCI company understand ANY concerns with the approach you see.
- Ultimately – find the single question to place in your conclusions about acceptable to be CAPABLE and EFFECTIVE at handling the APIs they are under contract to handle. Be sure in question 66 to document whether the OEL handling approach aligns between the companies.
- One of the most common findings is we really don’t know whether exposure control is acceptable – write the finding to have the company secure the data to ensure their existing control strategy is supported.
- ALWAYS – reference what you SAW in the field, not what you read in a SOP. Be sure to document what you did or did not see on your tour! SCOPE toured is very important for possible sharing of future audit reports between PSCI members. For example we did not see the highly potent handling area or we did not tour buildings 1,2,3.

Using the PSCI Questionnaire for IH

Safety Questions – for IH

- 49. Have any significant Health & Safety incidents occurred at this facility over the past three years?

Some Ideas/Considerations

- Request incident investigation and evaluate the content to identify if investigation was able to identify the root causes.
- Verify that the action plan was effectively implemented or is in progress to be implemented in a reasonable amount of time.
- Verify that event root causes are not observed through your field visit.

- 50. Does the facility provide the following types of HSE (Health, Safety & Environment) training to employees (full-time, temporary, or contractor)?
  - Hazard Communication
  - Personal protective equipment & Respirator use
  - New Employee training
  - *ASK about contractors*

Some Ideas/Considerations

- What is the company policy for providing Hazard Communication training? Are they following their policy? How employees are able to get chemical hazard information during their work?
- During your visit,
  - get the names of employees working with chemical substances, wearing PPE and respirators and cross reference if they have been trained.
  - request some of the employees to get the SDS of a chemical substance and explain you the hazards of the substance.

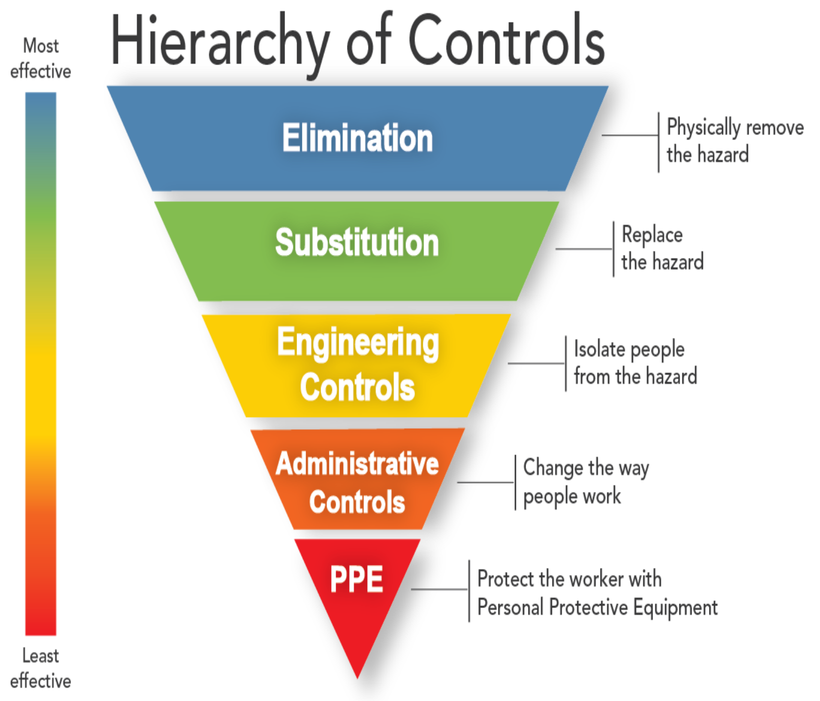
PSCI Occupational Health/IH Questions

Risk Assessment and Exposure Controls Capabilities

- **65. Does the facility perform risk assessments for chemicals handled?**

Some Ideas/Considerations

- Review site risk assessment and identify that:
  - Hazards are identified,
  - Occupational exposure limits are available,
  - preventive or protective measures were identified and are in place to control the risks.



- **67. Has the facility established exposure control capabilities for handling pharmaceutical compounds? Have OELs and control strategies been assigned for all APIs, raw materials and intermediates?**

- **73. Does the facility rely primarily on respiratory protective devices and/or engineering controls to protect employees who handle chemicals to achieve exposure levels below the OELs?**

1 – Actual IH Questionnaire questions..

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Occupational Health and Industrial Hygiene			
65	Does the facility perform risk assessments for chemicals handled?	Yes ☐ No ☐ Please explain: Do they consider pregnant women? Yes ☐ No ☐	Yes ☐ No ☐ Comments
66	Has the facility occupational exposure level (OEL) values for all Active Pharmaceutical Ingredients (API) and hazardous substances (including intermediates and solvents)?	Yes ☐ No ☐ NA ☐ If yes, please explain how the OEL values are obtained:	
67	Has the facility established exposure control capabilities for handling pharmaceutical compounds? Please specify the lowest control range of containment for dust/powder handling that has been achieved.	Yes ☐ No ☐ NA ☐ ☐ < 1µg/m³ ☐ 1-10 µg/m³ ☐ 10-100 µg/m³ ☐ >100 µg/m³ Comments:	
68	Does the facility perform risk-based medical monitoring or employee health surveillance which includes recording, investigation and follow-up?	Pre-employment physicals: Yes ☐ No ☐ Routine blood monitoring: Yes ☐ No ☐ Routine urinalysis: Yes ☐ No ☐ Lung function testing: Yes ☐ No ☐ Hearing test: Yes ☐ No ☐ Other: Yes ☐ No ☐ If yes, please describe:	

69	Has the facility developed and implemented a plan to protect First Aid Responders and Medical Professionals from exposure to body fluids?	Yes ☐ No ☐ Please explain: °°°°° Does the program include: Training? Yes ☐ No ☐ Exposure response kits regularly checked? Yes ☐ No ☐ The offer of Hepatitis B vaccinations? Yes ☐ No ☐
70	Does the facility perform exposure monitoring for the following health and safety risks?	Solvent vapors: Yes ☐ No ☐ NA ☐ Workplace noise levels: Yes ☐ No ☐ NA ☐ Pharmaceutical powders: Yes ☐ No ☐ NA ☐ Radiation levels: Yes ☐ No ☐ NA ☐ Oxygen-deficient atmospheres (e.g. nitrogen, inert gases): Yes ☐ No ☐ NA ☐ Ergonomics (height lifting, clima, illumination, vibrations, ...): Yes ☐ No ☐ NA ☐ Other: Yes ☐ No ☐ If yes, please describe: °°°°°
71	Is there a site procedure to inform employees of the results of exposure evaluations and monitoring results?	Yes ☐ No ☐ NA ☐ Comments: °°°°°
72	Does the site provide Personal Protective Equipment (PPE) for face, eye, foot, head, body and hand protection?	Yes ☐ No ☐ Please explain: °°°°°

73	Does the facility rely primarily on respiratory protective devices and/or engineering controls to protect employees who handle chemicals to achieve exposure levels below the exposure limit?	Respiratory protective devices Yes ☐ No ☐ Engineering controls Yes ☐ No ☐ Please specify the types of engineering controls used to manage identified chemical exposure risks: Laminar flow hoods: ☐ Down flow booths: ☐ Powder transfer systems: ☐ Alpha-beta valves: ☐ Split butterfly valve: ☐ Soft or hard wall isolators: ☐ Local exhaust ventilation: ☐ Closed processes: ☐
74	Does the facility use any of the following respiratory protection equipment for worker protection against exposure to chemicals or pharmaceutical compounds?	Supplied air breathing systems Yes ☐ No ☐ Powered air purifying respirators Yes ☐ No ☐ Full face respirators Yes ☐ No ☐ Half face respirators Yes ☐ No ☐ Filtering face masks Yes ☐ No ☐ Other Yes ☐ No ☐ - If yes, describe: What criteria are used to select respirator protection devices? Respiratory Protection is not used? ☐ Please explain if not applicable:
75	Are there provisions for fit testing, training, use, cleaning, inspecting, storing, and maintenance of respirators?	Yes ☐ No ☐ NA ☐ Please explain:

2 - Subject Overview &
3 – Problem Areas

Potent and Sensitizing API Compounds
What is a Good IH Program?

- An onsite person who has had training in control of hazardous agents.
- Access to an expert (e.g. certified industrial hygienist, qualified consultant).
- Inventory of hazardous chemicals, in particular potent materials, sensitizers, carcinogens and reproductive hazards.
- Information on chemical agents from customers and suppliers, occupational exposure limits or use of a banding system.
- Access to SDS and communication of risks, procedures and controls to staff using the hazardous chemicals.
- Risk assessments:
  - chemicals used, operations performed, assessment of control measures (including non-production tasks such as maintenance of equipment, handling of waste).
  - physical hazards and exposure controls methods in place.
- PPE Procedures and training on use, storage, and cleaning.
- Exposure sampling and monitoring data as appropriate.
- Risk based health surveillance.
- Incident/exposure records.
- Company has default program rules for unknown characterized chemicals.
- Worst case scenarios are understood for off-site consequences with training and emergency plans that are practiced….e.g. Ammonia cloud going off site.

WHY is this so critical in Pharma?
Because APIs are not Nuisance Dust

INDUSTRIAL HYGIENE / WORKER EXPOSURE RED FLAGS

- Look at SDS between companies – do they agree on OEL and classifications? Differences >20X are of concern.
- We know APIs do not have regulatory exposure limits – PSCI companies DO NOT treat APIs as NUISANCE DUST. Agree on the required exposure limit and control banding. If none exists – Red Flag.
- API /DP companies for Pharma MUST have internal processes for setting final API and intermediate control banding and implementing those practices – especially in development and for intermediates.
- Industrial hygiene workplace monitoring needs to CONFIRM their strategy is working, especially when exposure limits are low and PPE in use is very minimal. No data is a RED FLAG.
- IH Capability in some parts of the world is a challenge. We typically encourage our partners to hire consultants.

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Building responsible supply chains

PSCI Audit Findings Definitions

Critical Findings:

- Are **very** high risk findings that require immediate action to protect human life, the health of employees or the environment;
- May result in loss of license to operate or serious damage to reputation;
- Require immediate corrective action by the supplier;
- Need to be communicated to the audit sponsor prior to audit report finalization.

Examples for critical findings:

- Severe violations of human rights or labor rights (e.g. presence of child labor in a facility or forced labor, over-excessive working hours);
- Health and safety issues that can cause immediate life threatening situation or serious injuries to employees and other individuals on site;
- Environmental or safety issues that could result in serious and immediate harm to the community.

Other findings:

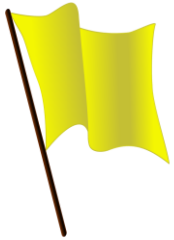
- Are all other major or minor audit findings, which need to be corrected by the supplier in an appropriate period of time?

IH Red Flag

Potential IMMEDIATE Concern

- Site handling their API as NUSIANCE DUST 10 mg/m3 because no regulatory limit. No banding approach exists for products without limits.
- Site has never seen the API – OEL from the PSCI member company SDS. When you compare SDSs available, there is a major difference in classifications and OEL.
- Highly potent pharmaceutical being handled (<10 mcg/m3), operation is OPEN , respirator required by SOP but is NOT on the site or completely wrong for the hazard class (e.g. not a respirator or respirator protection factor too low). No segregation and unsure if nearby personnel are also overexposed.
- During tour of area with highly toxic gases and/or solvents – you smell strong odors, experience irritation, see wrong PPE, and no alarm or shut-offs. Dust masks being used on solvents/gases.   Process venting is directed into the room where people work.
- The site lacks any data to justify that they know their workers are protected. This combines with limited or no Hazcom information and PPE practices.
- Site performs QC sampling in warehouse on the open floor for ALL chemicals.
- There is no LEV in the centrifuge unloading or dryer loading rooms where wet cakes are being handled. Limited PPE is being worn.
- No capable resource being used to manage IH issues/concerns.
- There is NO IH sampling data for any process or chemical on record.
- IH monitoring (if collected) has had faulty interpretation – there are clear overexposures and no action.

IH Red Flags – PSCI "Other" type of examples



- IH Program in place but some minor differences between OELs and Protection factors between companies.
- PPE and IH Program are written centrally by API company – instructions on posters, SOPs, etc., do not match what is available at the actual site. Need confirmation of all SOPs and PPE actual requirements so workers can be protected. No evidence of immediate overexposure concerns.
- Site not doing respirator fit testing
- Site has not linked occupational workplace exposure to their health surveillance program fully
- Combination of all controls appear to be protecting workers but process is HIGHLY dependent on PPE and administrative controls. Engineering improvements to improve control are strongly recommended.
- Site has not assessed exposure risk and potential in lab areas handling OEB 4/5 materials.
- IH data collected is very limited, all area samples (no personal results)
- LEV exists, but designs and photos show it is most likely highly ineffective to control risks and no (or very minimal) PPE is being used. The site needs a review of its engineering control strategy and data collected on LEV/exposure performance…no potent compounds.

First Question to prepare before audit – Do we agree on Hazards of API? Do we agree on the Controls Needed?

- API Supplier – Generic
- API Supplier – Proprietary Chemistry as Contract Manufacturer
- Pharma Drug Product site acting as Contract Manufacturing Company

Some Ideas/Considerations

- Review SDSs available– Do they agree on Hazard Classification and Occupational exposure limit?
  - If there is different classification or different OELs, Are the implemented exposure control methods based on the most conservative/lowest OEL?

- In your field visit, verify which are the exposure controls in place. Do they match with the described in the Risk Assessment?
- Request results of IH monitoring data collected.
  - If monitoring has not been conducted, verify exposure control/containment capabilities in your field visit.

Other MSDS Classification Issues

- Material is a Dangerous Good for Shipping and API company is not aware of the toxicology data driving this decision
- Packaging, Shipping, and handling practices need awareness
- If shipped to EU, CLP product labeling for some products (e.g. feed) may be impacted.
- Combustible Dust Classification
- Process Safety Data may not may not be on the SDS depending on the company philosophy.
- Labeling for receiving customer country and shipping country

A few foundational basics….

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- **Occupational Exposure Limit (OELs)**
  - A numerical air concentration limit expressed as PPM or mg/m3 over a stated time duration (8hr, 12hr, 15 min, Ceiling) which nearly all adult workers may be exposed to during their working lifetime without adverse effects. These may be set by a government or a company.
  - Thousands of chemical do NOT have OELs.
  - Can be found on a SDS.

- **Occupational Exposure Banding** – Pharmaceutical Industry Method
  - Classify the Hazard Bands and pick your Default Band: The method a company establishes to setup rules for identifying a control strategy for handling materials with limited toxicology data for safe handling. The bands may be created using rule sets, limited toxicology, and Risk Phrases from the Global Harmonization Standard. Typically found on a SDS.
  - An established set of recommended ENGINEERING and CONTROL strategies for handling chemicals within a chemical exposure band. Companies who set OELs generally have these. NOT typically found on a SDS.

$$\text{OEL } (\text{mg/m}^3) = \frac{\text{NOEL } (\text{mg/kg/day}) \times \text{BW (kg)}}{\text{V } (\text{m}^3/\text{day}) \times \text{S} \times \text{UF} \times \alpha}$$

- NOEL = the no-observable-effect-level (mg/kg/day)
- BW = average human body weight (50 kg)
- V = volume of air breathed in an 8-hr work day (10 m^3/day)
- S = time, in days, to achieve a plasma steady state
- UF = uncertainty factors
- α (alpha) = % absorbed through inhalation

On Line Control Banding Information and Tools

- COSHH (Control of Substances Hazardous to Health) Essentials (UK HSE, 2006)
  http://www.coshh-essentials.org.uk/
- ILO (International Labour Organization) International Chemical Control Kit (ILO, 2006)
  http://www.ilo.org/public/english/protection/safework/ctrl_banding/index.htm
- AIHA Control Banding Working Group
  http://www.aiha.org/content/insideaiha/volunteer+groups/controlbanding.htm
- NIOSH Control Banding
  http://www.cdc.gov/niosh/topics/ctrlbanding/
- ISPE Volume 7 (2010) "Risk Based Manufacture of Pharmaceutical Products"
- PSCI website – Type in "IH, Banding, or Containment" on the resource link.

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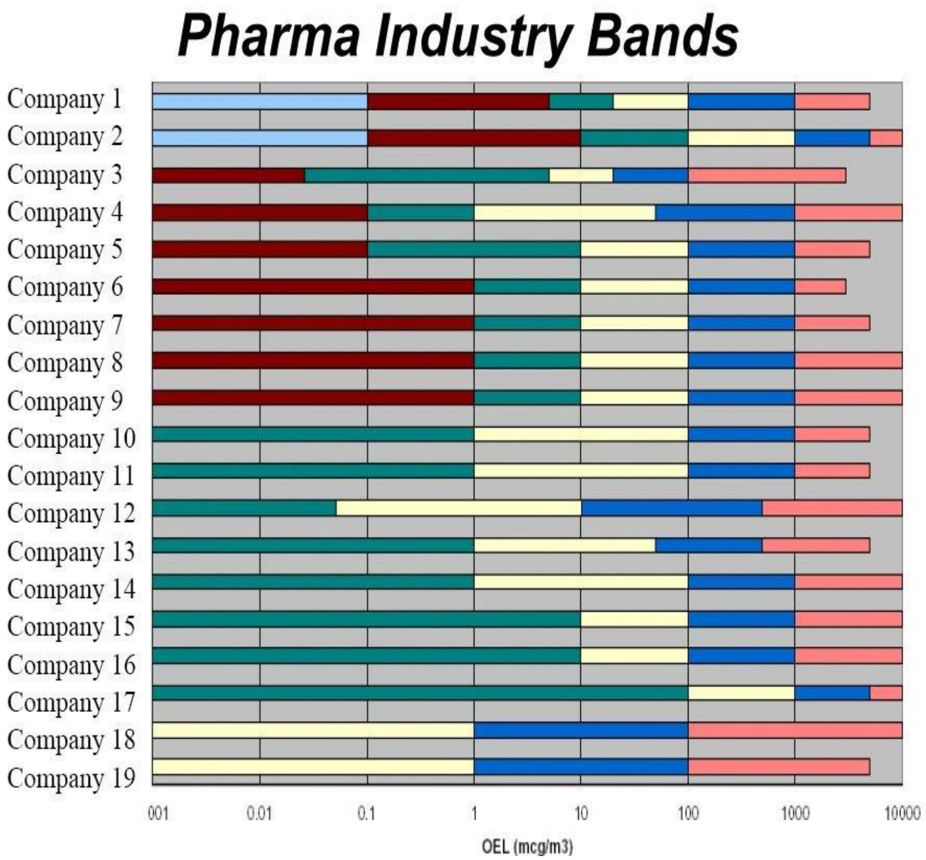
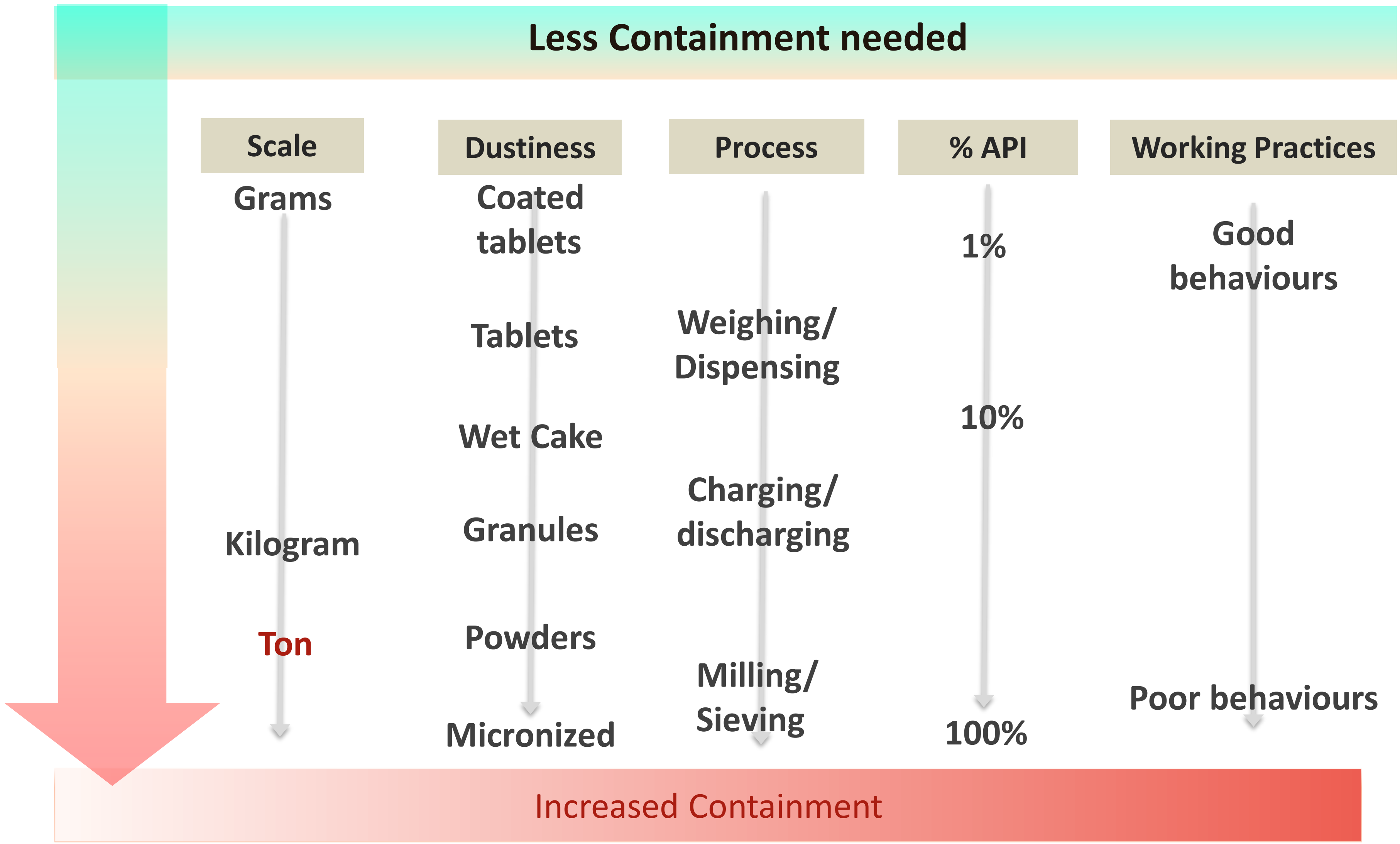
- Example of exposure control banding:
  - OEB 1 (>1000 ug/m3)
  - OEB 2 (100-1000 ug/m3)
  - OEB 3 (10-100 ug/m3)
  - **OEB 4 (1-10 ug/m3)**
  - **OEB 5 (<1 ug/m3)**



Yes –variation does exist among companies.

Managing Potent and Sensitizing Compounds
Factors Influencing Exposure



Factors Influencing Exposure

If you are Auditing a Company with OEB 4/5,
you really need experience with Exposure control concepts.

Are the controls identified in the Risk Assessment appropriate for the substance OEL or Band and the operation or task observed in your Field visit?

Engineering Control Capabilities from PSCI website

Engineering Control	OEL Capability (µg/m3)*
Walk-in fume hood	< 5000
Laminar flow booth (horiz)	< 500
Laminar flow w/ continuous liner	< 100
Downflow booth	< 100
Downflow booth w/ screen	< 25
Split butterfly valve (SBV)	< 10
Single chamber glovebox (GB)	< 1
SBV w/ purge capability	< 0.5
Glovebox isolator around continuous liner	< 0.1
GB w/ RTP (rapid transfer port)	< 0.05
Multi-chamber GB w/ RTP/ESBV	< 0.01

** operator exposure during unit operation*

Isolators

High Containment Capability for Potent Substances/APIs.

Flexible- glovebag

Rigid- glovebox

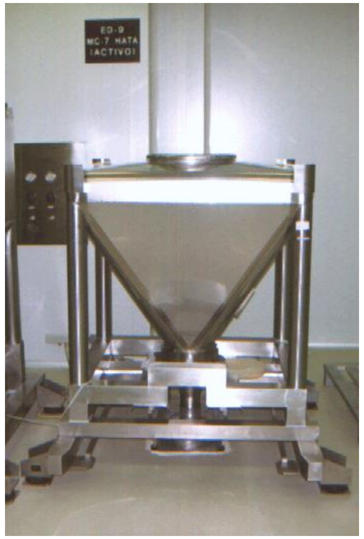
Laminar Flow Booths

When working on Laminar Flow Booths, additional control measures are usually needed to handle potent APIs.

Another important aspect is to ask how filters are changed/replaced? Is it performed in a way that minimizes exposure potential ?

Material Transfers

vs



Active- open

Might be acceptable for substances with high OELs, non Potent.

Active- closed

Appropriate for potent substances or substances with low OELs.

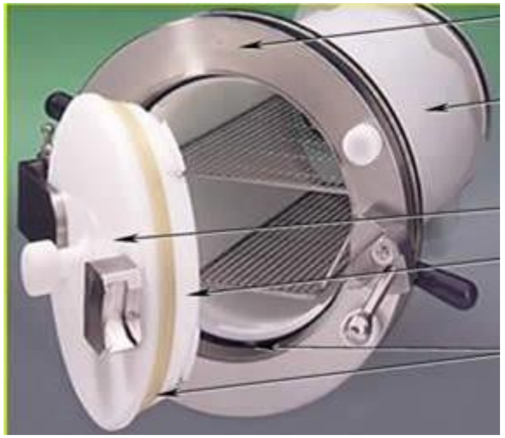
IBC

High containment design but transfer mechanism has to be set in place according to the substance containment level.

FIBC

High containment design for potent and low OELs substances.

Containment Transfer Mechanisms



Alpha/beta flange

Cone valve

Split Butterfly Valve

Containment flap

Continuous liner

Cut & tape bag

Local Exhaust Ventilation (LEV)
Good vs BAD Design

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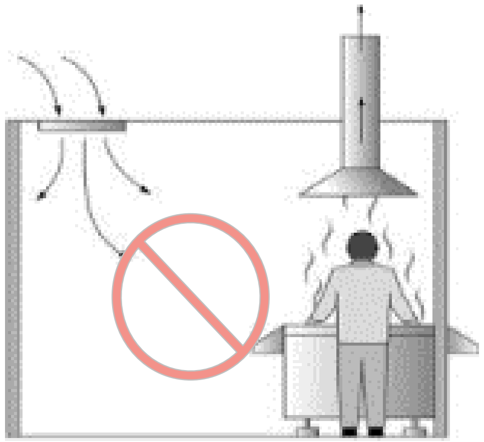
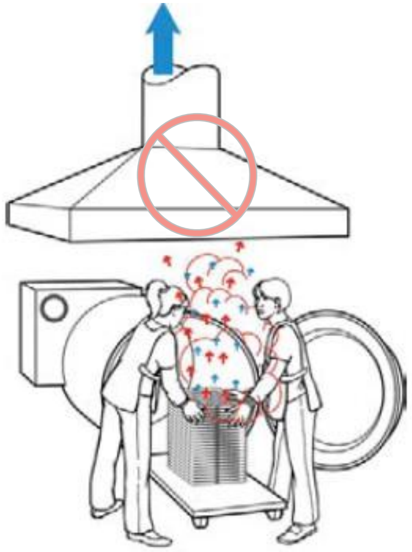
PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

BAD Design Examples





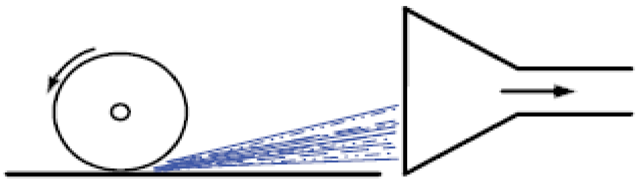
Dust are passing by employee breathing zone.
As a general rule in Industrial Hygiene, Canopy hoods shouldn't be used for dust emission processes.

Local Exhaust Ventilation (LEV)
Good vs BAD Design

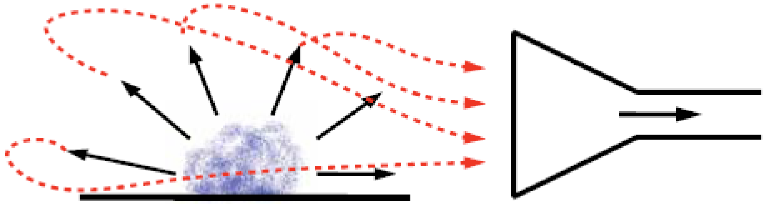
- Receiving and Capturing local exhaust are more appropriate for dust, gases, vapors, and fumes emissions when LEV design meets face and duct velocity industrial ventilation parameters (such as ACGIH Ventilation Manual).
- As a general design rule, emission source shouldn't be farther than 1.5 duct diameter of the hood face.
- LEVs has showed use limitations for potent or low OELs substances, especially when high quantities are handled.

Good Design Examples

Receiving



Capturing



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Good vs BAD Design?

Caution:
When handling Potent APIs, this would not be acceptable. Usually the human eye can not see dusts levels < 10 ug/m3.
Therefore, IH monitoring is necessary to assess containment capability and exposure potential – even on what you think might be well contained

Request IH monitoring studies.

- Is it appropriate for the type of operation or substance containment level?
- Does it has the appropriate duct and face velocity?

Request duct and face velocity and compare with industry standard (eg. Industrial Ventilation Manual).

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Laboratory Controls

Fume Hood

- Average face velocity 100 fpm
- Max sash height should be demarked
- Alarm (face velocity loss)

Biological Safety Cabinet

Ventilated Enclosure Cabinet for Weighing

- Face velocity varies between 75-100 fpm depending of the cabinet type.
- Alarm (face velocity loss).
- HEPA filtration or ducted models available.
- Filter integrity testing.

Employees must be Trained on how to appropriately use these equipment.

Request performance testing and compare results with industry standard or manufacturer recommendations.

Laboratory Controls

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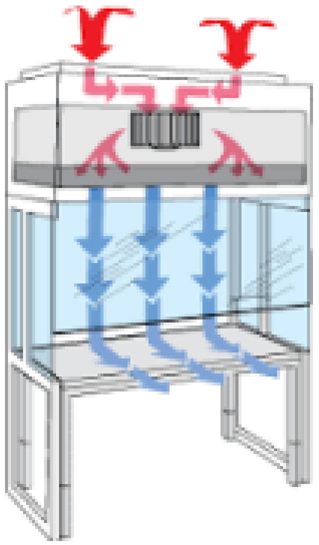
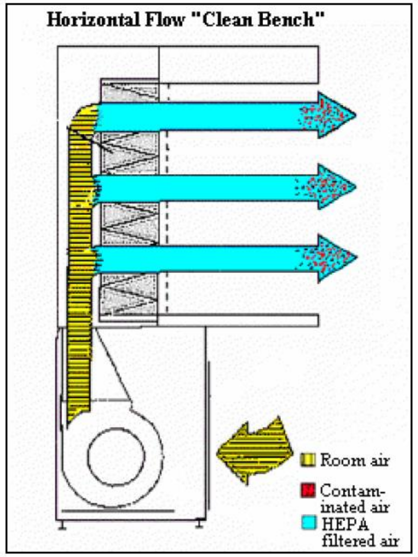
Glove Box

- Provides High Containment capability
- Requires detailed procedure to describe
  - Pre inspection verification
  - Practices for removing API and material (reusable and no reusable) after its use.
- Requires routine maintenance (gloves replacement, filter, pressure test).

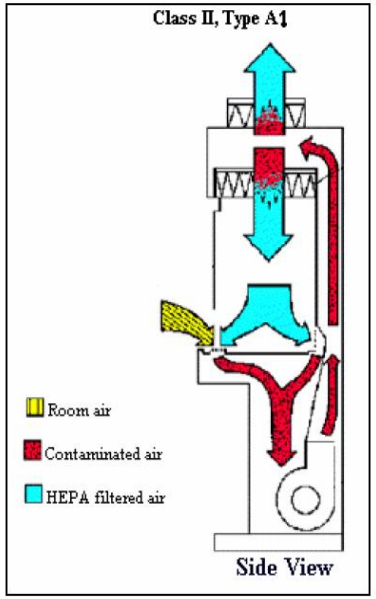
Laboratory Controls

Laminar Airflow Bench





Biological Safety Cabinets

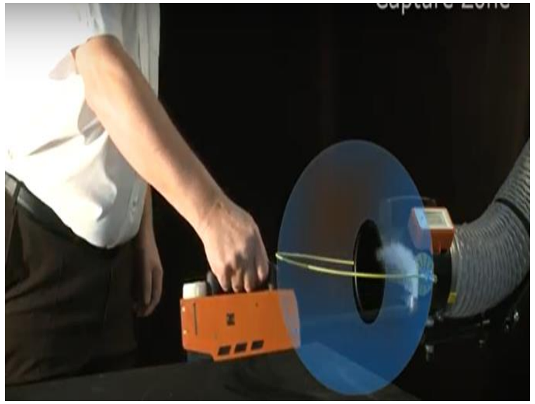


<u>Caution:</u>
Laminar Airflow Workbenches does not provides worker protection.

Biological Safety Cabinets Type I or II provides personnel protection.

http://www2.tulane.edu/oehs/safety/upload/BSCFactSheet-2.pdf

- Proper function of engineering controls depends on adequate maintenance.
  - **Request maintenance records for all engineering control methods and check equipment are being tested in a regular basis and results are compared with industrial standard parameters or manufacturer design parameters.**



Other IH Considerations in Laboratories

- Chemical Storage by Compatibility (Acids, Bases, Oxidizers, Flammables, Health)
- Flammable Cabinet Storage

- Availability of Eye Wash Safety Showers

IH Monitoring Basics

70. Does the facility perform exposure monitoring for the following health and safety risks? Mark per category.
71. Is there a site procedure to inform employees of the results of exposure evaluations and monitoring results?

- Do data/studies ONLY focus on API and not on solvent/gases – Can be BIG issue for wet cakes in API plants.
- Evaluate:
  - # of samples, # of days sampled to understand exposure profile distribution
  - Total Dust vs API dusts at Drug Product Sites – if they are estimating are they using math?
  - Personal Breathing Zone Samples vs Area Samples
  - Short tasks data versus full shift data
  - Training or Technical expertise of the person that
    - collected the samples
    - make study exposure conclusions, and
    - report writer
  - Verify the Math on protection factors
  - No data – they use company's commissioning data on their web site.
- Employees should be informed of monitoring results.

Is it well managed?

Does it seem appropriate?

Most important, use the information to <u>qualify the scope of the data you did see.</u>

Reviewing IH Monitoring Data

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During the review of the IH Information and Monitoring Data:

- Be very careful of Units of Measure:
  - mg/m3
  - mcg/m3=µg/m3
  - µg/m3
  - ng/m3

Example:
API Manufacturer Limit : 0.1 mg/m3

PSCI Member Limit: 0.1 mcg/m3

Banding Exercise
What mass can your eyes no longer see?

Average worker breathes about 17 m^3 in a workday

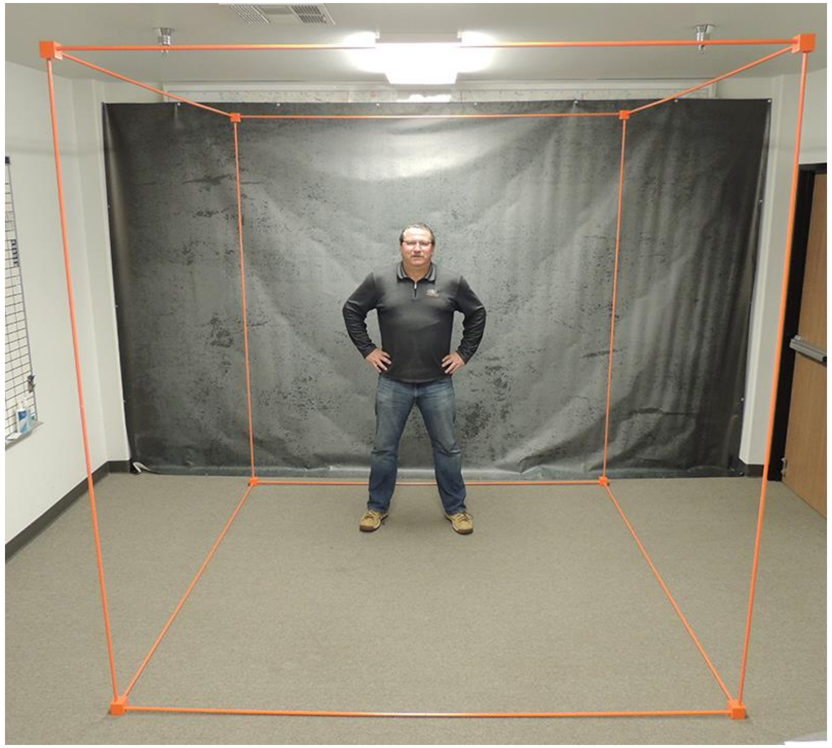

Photo from web reference "IP Powertools – Understanding the OSHA Silica PEL"

Band Range	Mass inhaled over 8hr day
10,000 μg/m^3	4% sugar pack
1,00 μg/m^3	0.4% sugar pack
100 μg/m^3	0.04% sugar pack
10 μg/m^3	0.004% sugar pack
1 μg/m^3	0.0004% sugar pack
0.1 μg/m^3	0.00004% sugar pack

Processes or Steps with High Potential of Exposure

- Reactor charge/material transfer
- Drying/discharging
- Granulation/mixing
- Milling/de-lumping
- Compression
- Dispensing/weighing/repackaging
- Maintenance activities
- Cleaning / Heel Removal
- Process upsets/spills

Focus your tour to see these things

When doing a PSCI audit for a member company – Request their banding categories and tools.

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Example: Control Banding Implementation

Band	PPE	Facility Design	Engineering Controls	Equipment Cleaning and Maintenance
Level 1	•Gloves •uniforms	•General Ventilation •Shared HVAC •General Filtered Exhaust •Recirculate Permitted •Common Gowning & De-gowning	•Passive Ventilation/Dilution •Open Mat'l Conveying and/or Mat'l Transfers •Open Process Equipment	•Open Process Equipment Transport to Cleaning Area •Manual Cleaning
Level 2	•Respirators •Tyvek coveralls	•Pressure Differential To Selected Adjacencies •Open Process Area •Closed Building •Process segregation with doors •Gowning/De-gowning Room	•Standard Equipment Design (Normally Closed) •Local Exhaust Ventilation •Mat'l Conveying Essentially Open with Hardware Remediation •Pressure Convey •Laminar flow	•Open Process Equipment Cleaned In-Situ
Level 3	•Maximum PF respirator	•HEPA Filtration •Room Finishes & Surface MOC's and Utilities Are Designed for Ease of Cleaning •Process segregation with airlocks •Decon Shower	•Standard Equipment Design with Separate Mechanical Space •Glovebox or Glovebag •Closed Material Conveying •Minimize Make/Break Connections •Split butterfly valves (SBV)	•Provide CIP with Rinse Water Capture •Closed equipment maintenance capability
Level 4	•Seek expert assistance •Respirators not adequate for "open" processing •Redundant PPE with engineering controls	•Seek expert assistance •Dedicated HVAC •HEPA Filtration w/Safe Change •No Exhaust Return •Closed Process Area •Closed Building •Separate Gowning & De-gowning •Automation	•Seek expert assistance •Process Equipment iDesigned for Total Containment •Closed Mat'l Transfers with Barrier Add-ons •Vacuum Convey •Minimize Mat'l Conveying Steps •Minimize Material Transfer Connections •Isolator with continuous liner •Enhanced/purgable SBV	•Seek expert assistance •Minimize Waste via Process and Formula Optimization •Protective barriers for laptops, paperwork, documents

2^{nd} question – based on controls in place, are people protected?

- If what you saw didn't use the Hierarchy of Engineering Controls, but was more heavily reliant on PPE or work procedures….
- ARE THEY ADEQUATELY PROTECTIVE?

72. Does the site provide Personal Protective Equipment (PPE) for face, eye, foot, head, and hand protection?

- Do PPE and Containment designation comes from a risk or hazard assessment?
- Are PPE and Containment requirements documented in the manufacturing ticket or batch record or employees are aware of the requirements by any other formal process?
- Are personnel wearing the correct/required PPE?
- Does the site's Respirator Program appear to be adequately managed?
- If the site is handling highly potent API powders or drug products, have they implemented containment measures to avoid "open handling"? Is there an actual engineering improvement plan? Does the engineering/containment plan comes from a risk assessment or IH monitoring results?
- If the site is handling potent API powders or drug products, have they implemented a comprehensive Industrial Hygiene Monitoring Program (i.e. more than just cursory area samples or particle counting)?

PPE Program should cover the following elements:

- Hazards and PPE types:
  - Head Protection
  - Eye Protection
  - Hearing Protection
  - Respiratory Protection
    - Fit Testing
    - Filters/Cartridges (Use and Replacement)
  - Hands Protection
    - Based on Compatibility Data (Breakthrough time)
  - Body Protection
  - Feet Protection

- Inspection of PPE
- Use of PPE
- Maintenance
- Cleaning
- Storage
- Training

Respirators

- There are two types of Respiratory Protection:
  1. Negative Pressure
  2. Positive Pressure

Negative Pressure

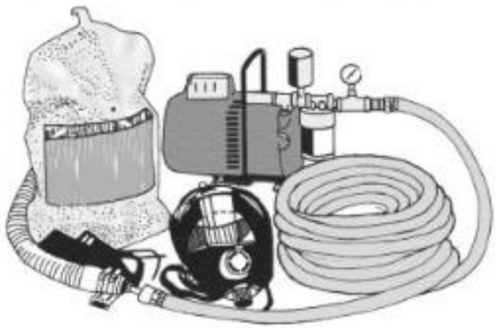
Half Mask Tight Fitting

Medical surgical mask is not a respirator

Full Face Mask Tight Fitting

Positive Pressure

Powered Air Purifying Respirator (PAPR)
Supplied Air Respirator
Self Contained Breathing Apparatus



Respirators

Negative Pressure	Positive Pressure
• Fit Test is conducted prior to assign. 	• Fit Test is not needed.
• Fit Check is conducted prior to use. Explained in Training. • Can not be use with beard or other interferences on the respirator seal. • Training is needed.	• Prior to use inspection is required (physical, battery, airflow, filtration media) • Training is needed.

Use of appropriate filtration media according to the chemicals present.

3rd Question – do we have adequate Respiratory Protection?

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The values of the APF in EU and other countries [edit]

Studies of respirator's performance was carried out not very often, and almost all of these studies were conducted in USA (and UK). It is possible that the lack of information about the RPD efficiency in the workplaces, was the reason behind developing these assigned PF in several European countries, whose values differ significantly from the evidence-based values of APFs in the US and UK.

The Assigned Protection Factors for some main RPD types, developed in several EU countries[2] [hide]

RPD type	APF in several EU countries			
	Finland	Germany	Italy	Sweden
FFP2 filtering facepices	10	10	10	10
Elastomeric half masks with P2 filters	10	10	10	10
FFP3 filtering facepices	20	30	30	20
Elastomeric half masks with P3 filters	-	30	30	-
Negative pressure air-purifying respirators with full face mask and P2 filters	15	15	15	15
Negative pressure air-purifying respirators with full face mask and P3 filters	500	400	400	500
Powered Air-Purifying Respirators (PAPRs) with loose-fitting hood or helmet, and THP3 filters	200	100	200	200
PAPRs with full face mask, and TMP3 filters	1000	500	400	1000
SARs with full facepiece and negative pressure demand air supply	500	1000	400	500
Supplied Air Respirators (SARs) with full facepiece and positive pressure demand air supply	1000	1000	400	1000
SCBAs with full facepiece and positive pressure demand air supply	-	≥ 1000	1000	-

If you see dust masks with open handling tasks this could be a red flag…

What is the Level of Protection

- The level of protection for Respirators is defined by the Assigned Protection Factor or Nominal Protection Factor.
- Usually, each Country has established their APF or NPF.
  - APF or NPF x OEL substance= Max Use Concentration

Application:

- Sampling results show a TWA of 350 ug/m3 in 8 hrs
- Respirator being used has a NPF of 10
- OEL for the API is 8 ug/m3 TWA 8 hrs

Is the Respirator appropriate?
> 8 ug/m3 x 10=80 ug/m3 (maximum use concentration).

No, Sampling results (350 ug/m3 TWA) are higher than respirator maximum use concentration.

Medical Surveillance

   

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68. Does the facility perform risk-based medical monitoring or employee health surveillance which includes recording, investigation and follow-up?

- Regulations can vary on formality of program and scope – <u>know your local countries requirements</u>
- Generally – programs globally exist for respirator protection, noise, some vaccines.
- Is there an occupational physician for the site who understands and sees the workers IH profiles and establishes the medical surveillance program?
- For highly potent compounds – does the site have any special medical surveillance programs, including biological monitoring?
- Has the site experienced high blood results / occupational health events – what is their response action?
- If the material is a sensitizer, has the site established processes to protect people with known allergies?
- How is the site managing reproductive hazards for both men and women?
- What is the frequency of IH Health type events at the site?
- How does the site investigate workplace exposure events?

Is it well managed?

Does it seem appropriate?

Does it cover all hazards that were identified in the visit?

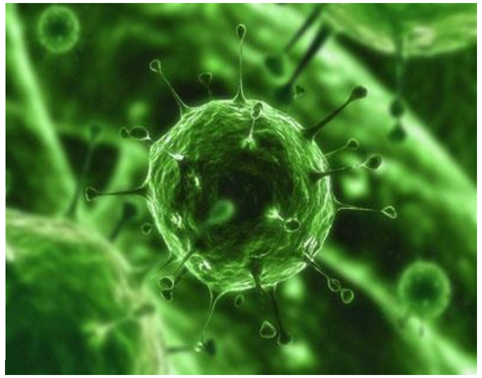
Case Study….potent steroid

- API manufacturer of Generic material did not set their own limits but found a limit on the web from another company and used it.
- **PSCI Member** limit was 500X times lower. Data exchange revealed similar thought process on setting limits but different toxicology data was being used. PSCI Member process allows for updating when new data available.
  - End Result – companies aligned within 5X on OEL accounting for different safety margin practices.
- Company had no workplace monitoring data to verify they were meeting their previous limit or the new limit. They were in a dedicated suite.
  - API company asked to immediately upgrade from dust masks and install better controls.
  - API manufacturer collected IH data to verify that their final PPE/engineering was protective.
  - Engineering controls were implemented in a very focused way reducing costs. Best practice ideas shared between member company and API manufacturer.
  - Company applying same approach to all their chemical manufacturing where OELs are not yet established.
- DATA IS YOUR FRIEND. In absence – default to more protective PPE & SOPs.

Biosafety & Radiation Safety

- Just as there are Control Bands for Chemicals, there are Risk Groups for Biosafety Hazards and the establishment of Biosafety Control Bands (1-4) for Biologicals. Do the companies agree?

- If sites have products with ionizing radiation and/or BSL 3 or 4 operations be sure the correct expert is part of the evaluation. Generally special government licenses may be required.



Writing good IH Audit Findings

Company has limited IH data…what to do?

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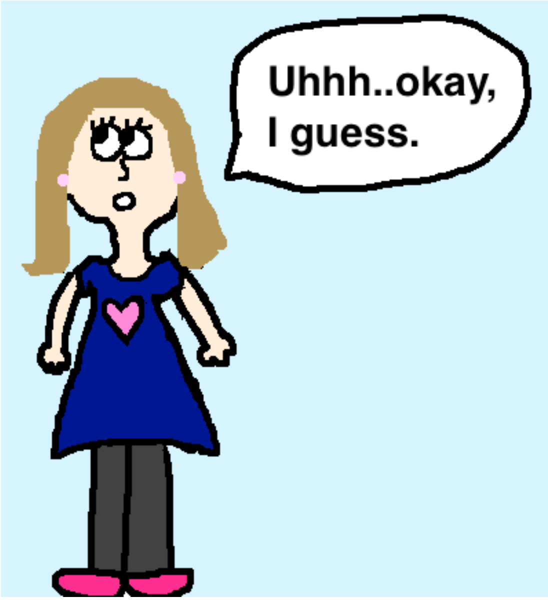
- Situation: API company hired IH consultant and measured total dust of one unit operation. Data for that one chemical on that one day showed the Respirator being worn was sufficient. Some containment in place and PPE and work practices generally seem to align to what you have seen of control bandings.

- Your PSCI member company has a different API of varying particle size/density and will use different unit operations at this facility that have not been sampled.

- Your PSCI member company requires data to support the control strategy but does not have an analytical limit to give the company.



Possible model finding: Company X lacks IH data to establish the effectiveness of their exposure control strategy. The following Unit Operations do not have IH data and a minimal protection factor of 50X is currently in use with a relatively open process.

Let's test our rating alignment
Is finding good and is this critical or "other"?

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Site is currently handling compounds with the highest hazard category of Containment (<1 ug/m3). As outlined in the IH (Industrial Hygiene) section of the SAQ, the following were noted as concerns over the handling of API.

- <u>Exposure Control Program Improvements</u>*
  - <u>Q 67. Site has a potent compound handling guideline they follow.</u> Site High potency lab and Facility X are capable for OEL <1 ug/m3 based on manufacturer data that was shared.
  - Q 70. Site lacks sufficient exposure studies on High Potency API & Low OEL Solvents for some tasks and chemicals (e.g., Methylene Chloride & API (Drying/Milling) to confirm PPE provides adequate protection.
  - Q 70/Q71. For IH worker studies in place, limited personal sampling exist and no statistical conclusions for exposure control are drawn. Data is highly variable and is not given to employees.
  - Q73. Respiratory Protection - Chemical cartridges are being used for some solvents where vendor does not support them as appropriate (e.g. MeCl2) an there are no cartridge change out schedule for filters and adsorbent cartridges (for other contaminants).
  - Q74. Lab hoods and LEV systems do not have routine PMs or performance testing. There are no safe change SOPs for the HEPA filters.
  - Q66. Site has not used the PSCI Member OEL in their risk assessment and has set their own limit which is 10X higher than the PSCI member limit.

  - With these findings – do you know what they do have in place?

Let's test our rating alignment

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Example Findings….How would you improve the finding. Is it critical or other?

- The site is using horizontal centrifuges for the isolation of intermediates and final API.
- The unloading of the centrifuges is done by removing the centrifuge bag with a hoist and shuffling the product out of the bag manually, leading to a certain exposure risk for the employees.
- In the finished goods warehouse several drums containing APIs were found contaminated.
- The auditee stated, that the will be cleaned (in the WH) before shipping.
- A customer complaint was issued in Dec. 2016 that yellow powder on the external surface of the drums.

The site currently uses hooded powered air purifying respirators (PAPR) for operators that will dispense, package, or handle material in the process area that will be used for the Customer product. The hooded PAPR has a protection factor of 25 (as specified by UK health and safety officials). Site personnel have not determined if this is adequate to protect operators that will handle our Band 4 compound.

1. About 20% workers who contact hazards noise and chemicals did not wear PPE e.g. not wear earplug/safety glasses in the foaming process.
2. At the chemicals preparation and mixing area, the factory did not provide chemicals-proof mask to worker as per the requirement

Observed from the examination report, one employee has the abnormal condition on the glutamic pyruvic transaminase in 2015 and 2017, but the facility does not take follow-up action. The employee is animal feeder.

Facility has no system to perform risk assessment for chemicals used in facility.

i) The Company is not maintaining the results of these exposure evaluations and monitoring results.
ii) Criteria for use of respirators i.e. Full/Half/ Filtering etc. is not defined for use as protection devices.

PSCI Auditor Training 2018

1) Emergency Preparedness and Response
2) Hazard Information

Benoit BARUTEAU

1 – AUDIT OVERVIEW

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Building responsible supply chains

Audit Questions Summary – Emergency Prepardness and Response / Hazard Information

Topic	Question summary
Emergency Preparedness and Response	• Fire detection/protection systems • Emergency response equipment inspection • Fire alarm system monitoring and notification to emergency services • Fire water for fire protection • Emergency exits and evacuation routes clearly marked, kept free of obstructions • Emergency exit signs illuminated with emergency backup power • Regular emergency evacuation drills • Emergency response plans • On-site emergency response team that is trained for fire or other emergencies
Hazard Informatio	

Topic	Question summary
Worker protection	• Does the facility have a safe work permit system **(Hot Work Permit)**

Topic	Question summary
Process Safety	• **Impact of its operation on the community** • **Safety measures around direct fire equipment (e. G. Boiler, incinerators, ovens etc.)**

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Topic	Question summary
Process Safety	• Impact of its operation on the community • Safety measures around direct fire equipment (e. G. Boiler, incinerators, ovens etc.)

78	Has the facility evaluated the impact of its operation on the community? Has the facility evaluated the impact from the activities of neighboring businesses?	Yes No NA Yes No NA	Yes No NA Comments
83	What are the safety measures around direct fire equipment (e. g. boiler, incinerators, ovens etc.)? *Consider gas accumulation, steam overpressure...*	Please describe:	Yes No NA Comments

1 – AUDIT OVERVIEW

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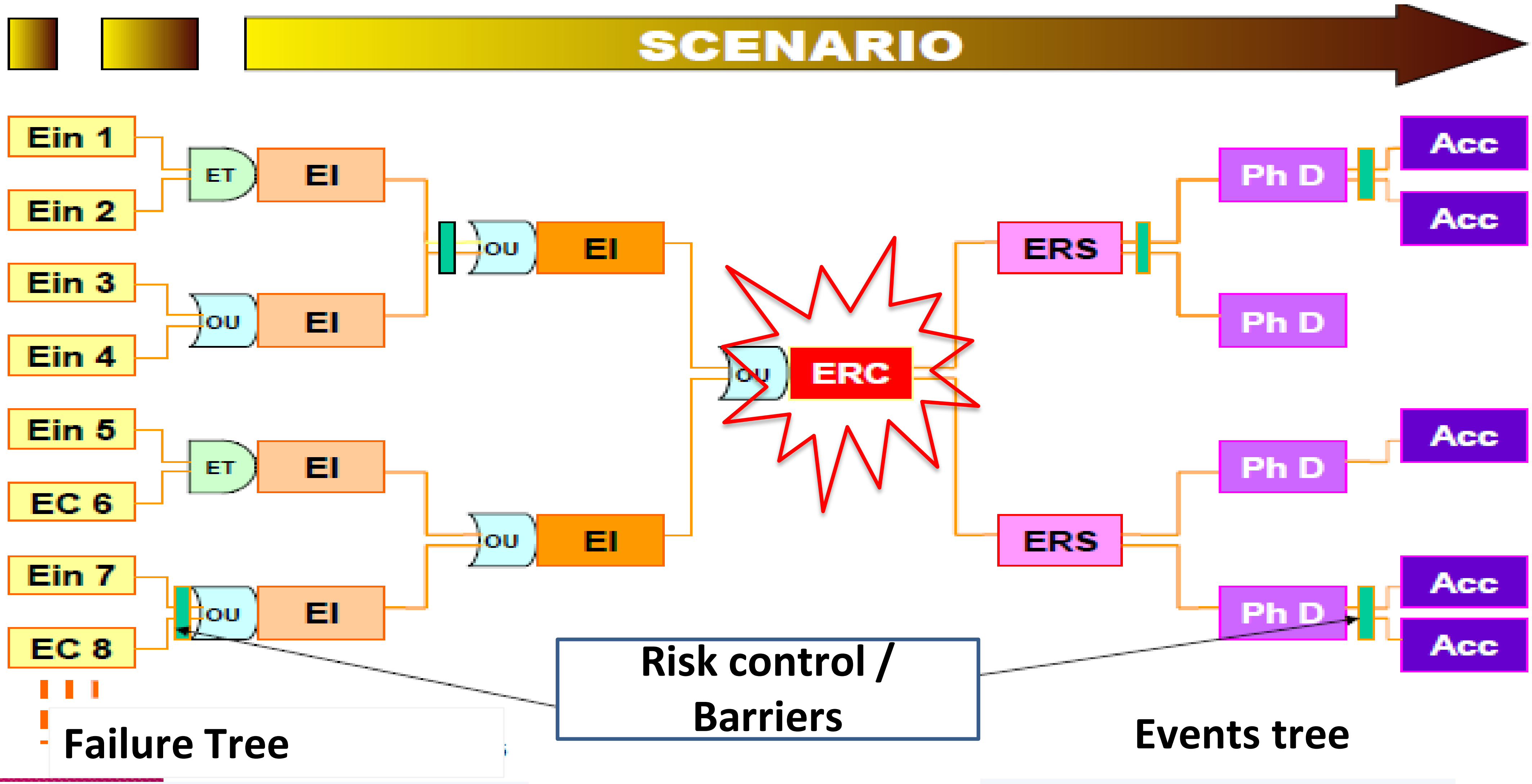

Emergency scenario: 3 types of effects

1 – Thermal effects : burns, suffocation

2 – Toxic effects: inhalation, intoxication

3 – Overpressure direct effets : Explosion of lungs or eardrums, Projection against an obstacle, …
Or indirect (missile effect): breaking of windows, moving objects…

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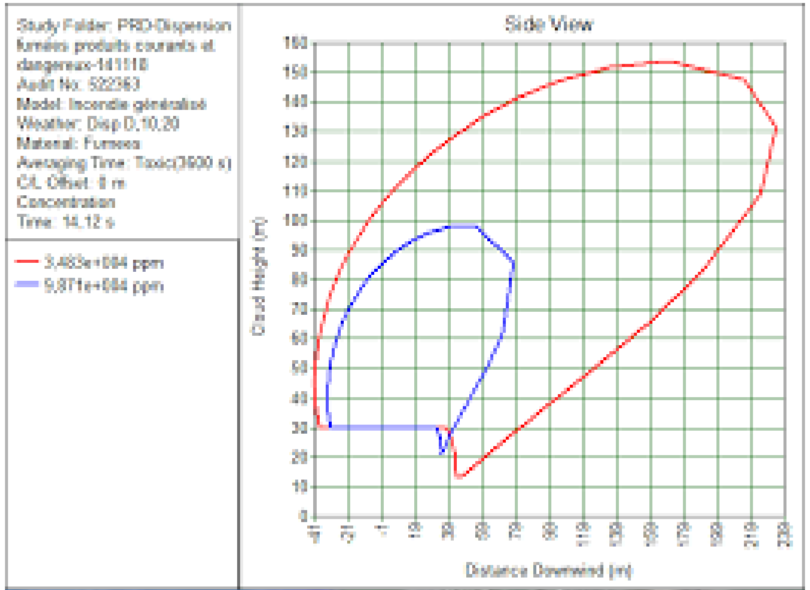
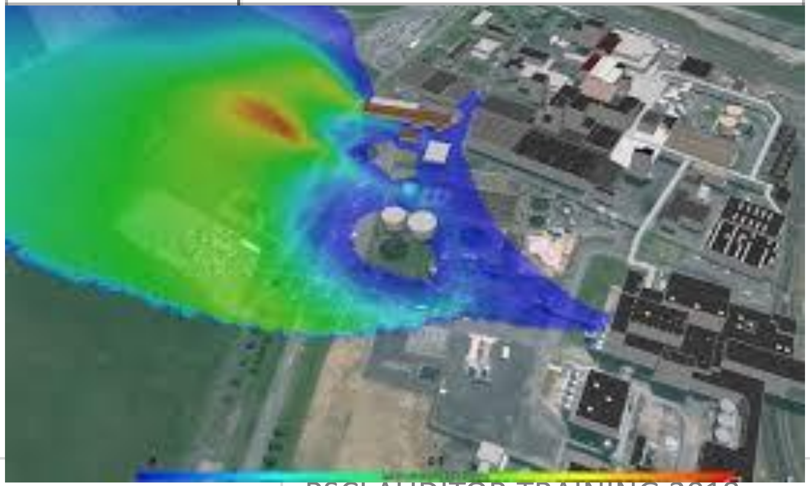
4 thresholds of effects on the people

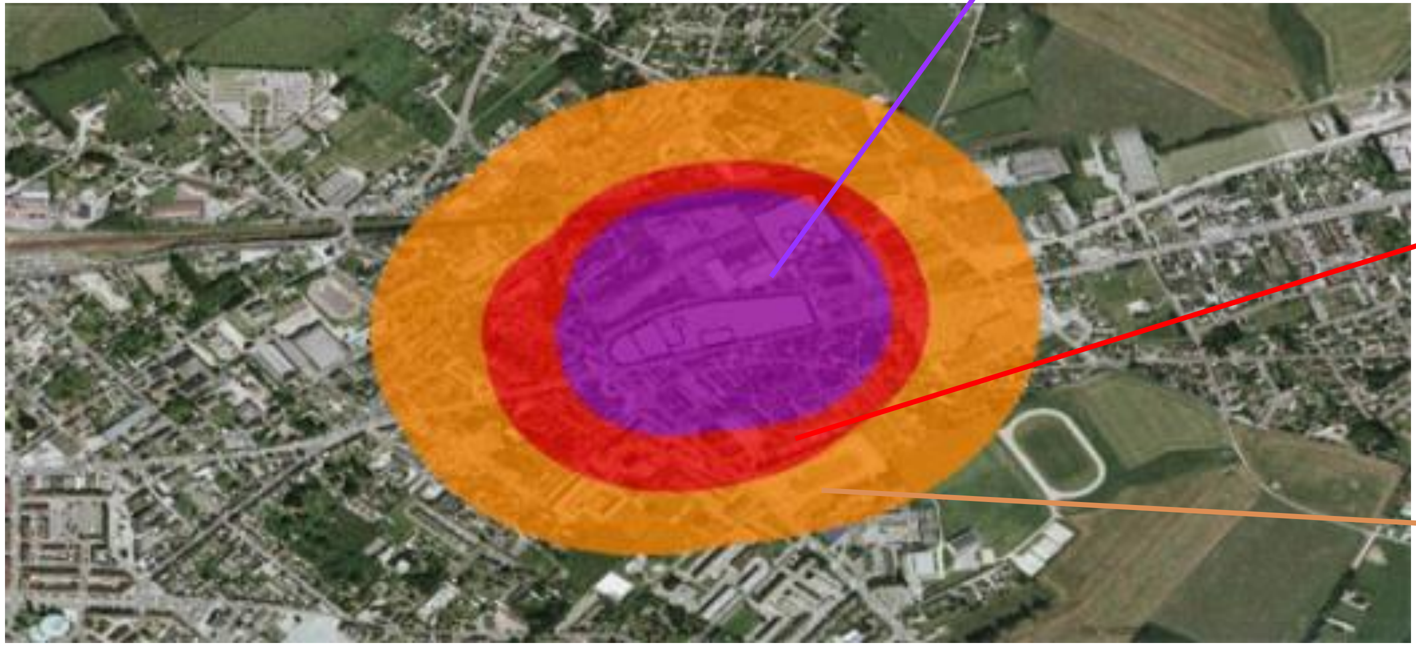
TYPES OF EFFECTS

Treshold of effects on human	Thermal	Toxic	Overpressure
LETHAL SIGNIFICANT (SELS)	$8 kW/m^2$	CL 8%	200 mbar
LETHAL (SEL)	$5 kW/m^2$	CL 1%	140 mbar
IRREVERSIBLE (SEI)	$3 kW/m^2$	SEI	50 mbar
INDIRECT (Breaking of windows)			20 mbar

Specific softwar calculation and graphiq representation







Zone of lethal significant effects

Zone of lethal effects

Zone of irreversibl e effects

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

Topic	Question summary
Worker protection	• Does the facility have a safe work permit system **(Hot Work Permit)**

55	Does the facility have a safe work permit system for the following?	**Hot Work: Yes No NA** Confined Space Work: Yes No NA Energy Isolation or Lock Out/Tag Out: Yes No NA Line Breaking: Yes No NA Work at Height: Yes No NA General Permit Yes No NA Other: Yes No Please describe:	Yes No Comments **AUDITOR GUIDANCE:** Provide the procedure title or # as reference and comment on the applicability at the site.

1 – AUDIT OVERVIEW

Topic	Question summary
Emergency Preparedness and Response	• Fire detection/protection systems • Emergency response equipment inspection • Fire alarm system monitoring and notification to emergency services • Fire water for fire protection • Emergency exits and evacuation routes clearly marked, kept free of obstructions • Emergency exit signs illuminated with emergency backup power • Regular emergency evacuation drills • Emergency response plans • On-site emergency response team that is trained for fire or other emergencies
Hazard Information	• Safety Data Sheets (SDSs) for all hazardous substances

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84	Are the following areas of the facility equipped **with fire detection/protection** systems?	Site areas	Fire/smoke detectors	*Sprinkler or suppression* systems	Comments AUDITOR GUIDANCE Briefly describe the site's fire protection program and to what extent it has been implemented. Describe any observations that could impair a normally acceptable fire protection plan in terms of building construction, fire load, general state sprinkler system, smoke detectors, alarm system, inclusion of key equipment in preventive maintenance program etc. Check for stored materials that could create a fire hazard, such as idle pallets.
		Raw material storage areas	Yes No	Yes No	Yes No Comments
		Flammable liquid storage tanks	Yes No	Yes No	Yes No Comments
		Process areas	Yes No	Yes No	Yes No Comments
		Finished product warehouse	Yes No	Yes No	Yes No Comments
		Hazardous waste storage area	Yes No	Yes No	Yes No Comments

85	Is the facility emergency response equipment **(fire extinguisher, fire pumps, sprinkler systems) visually inspected monthly,** comprehensively inspected annually, and documentation maintained for all inspections?	Yes No Please explain:	Yes No Comments
86	Is the **fire alarm system monitored 24 hours** a day (including weekends and holidays) with prompt notification to emergency services (within 5 minutes)?	Yes No Please explain:	Yes No Comments
87	Does the facility ensure that an adequate amount of fire **water is maintained for fire protection**?	How many cubic meters of fire water is maintained for fire protection? How was it determined to be sufficient? Can the capacity of the pumps meet the requirements of NFPA (sufficient water flow?) Yes No Please explain if No:	Yes No Comments

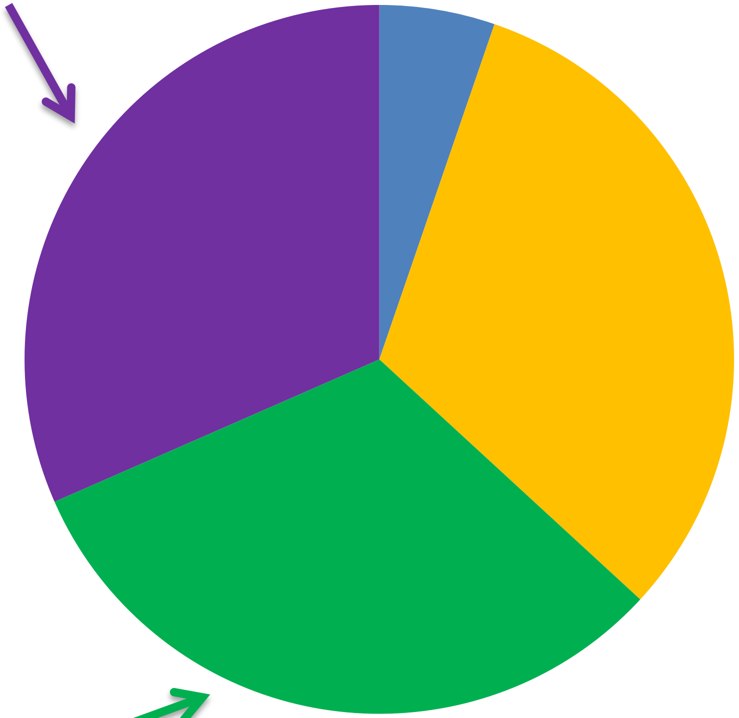
2 – SUBJECT OVERVIEW : FIRE SOURCES

SMOKING

>> Smoking policy

ELECTRICITY

>> Electrical inspection
>> Electrical rooms
>> Infra red – Thermography
>> Lightning protection



HOT WORK

>> Hot work Permit

PROCESS

>> Chemical :
process safety
>> Other activities : ??

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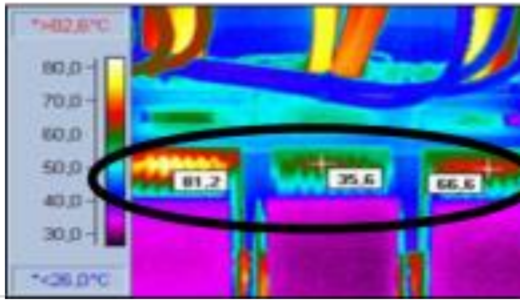
SMOKING

- Smoking policy specifies at the site entrance / visitor training ?
- Clear signs/ limits ?? To see during the site tour
- Do you find cigarette end during your site tour ?

ELECTRICITY

- Electrical inspection >> Maintenance / regular check
- Electrical rooms >> Visit electrical room, transformers PSCI 56
- Infra red – Thermography
  PSCI 56
- Lightning arresters
  PSCI 79
- Location of electrical equipments near combustible material ???



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PROCESS

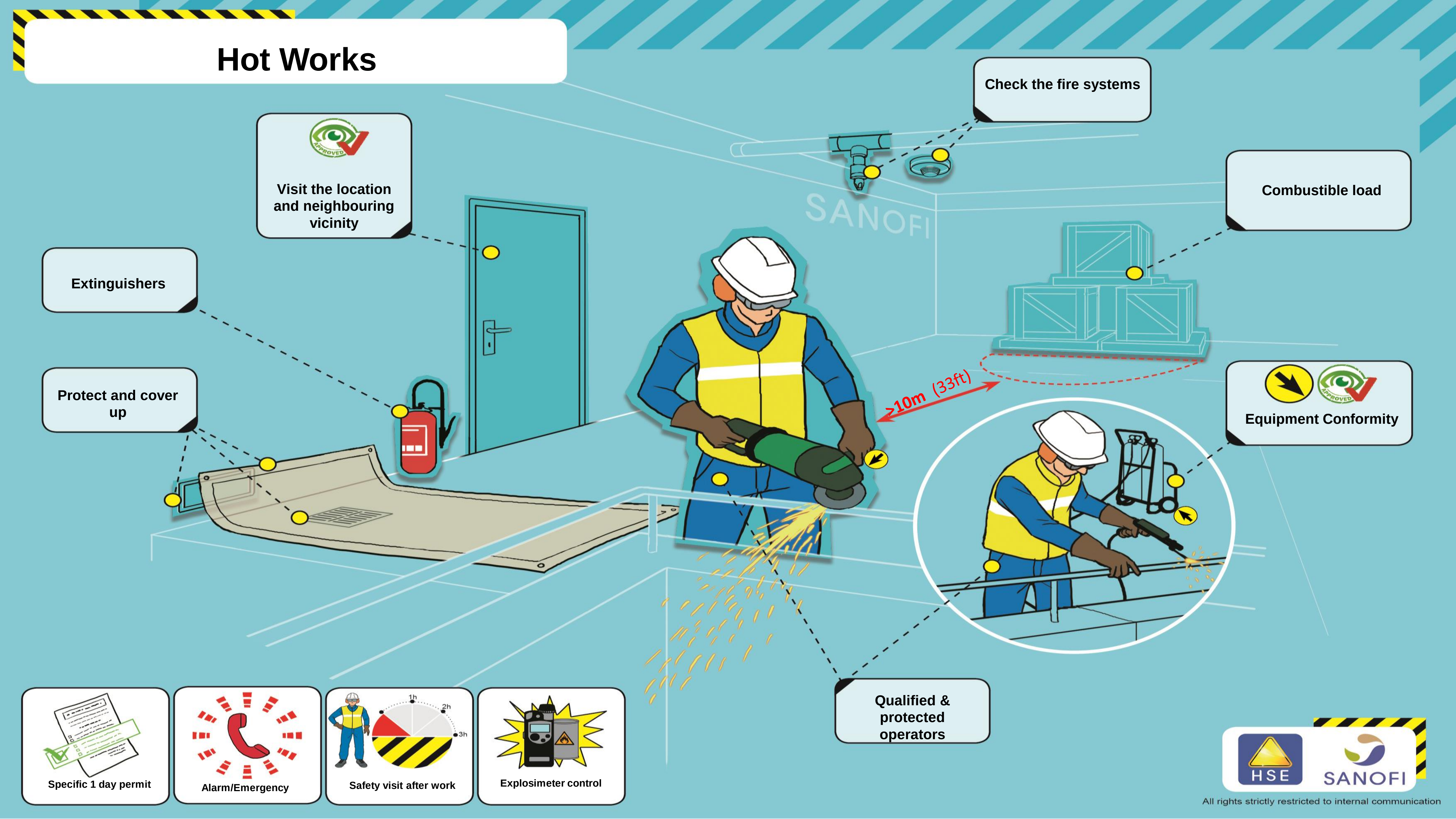
- Chemical/Pharmaceutical : process safety chapter — PSCI 76-82
- Warehouse:
  - Where are located the battery chargers ?
  - Lights above the storage /aisle ?
  - Stability chamber in Polyurethane / cooling system ?
- Pharmaceutical processes
  - Milling , Sieving, Micronization (see process safety / powder data)
  - Granulation (Use of solvant: see process safety)
  - Electrical dryer
  - Equipment running 24/7
- Laboratories:
  - Oven (24/7) CPLG: H2 ?
  - Mixing of waste …
- Technical area
  - Filters, Heater, Electricity

HOT WORK

during the documentation review :

- Check the Hot work Permit
- Procedures / SOP (link with HW Permit)
- Who signs hot work permit ?
- What if : Fire detection above the hot work permit ????
- Hot work permit in ATEX Areas >> LEL

- NO Fire detection >> Visit 1 to 3 hour after the end of the work
- **Permanently present for 1 hour.**
- **Patrols every hour for 3 hours**


Hot Works
Check the fire systems
Visit the location and neighbouring vicinity
Combustible load
Extinguishers
SANOFI
Protect and cover up
>10m (33ft)
Equipment Conformity
Qualified & protected operators
Specific 1 day permit
Alarm/Emergency
Safety visit after work
1h
2h
3h
Explosimeter control
HSE
SANOFI
All rights strictly restricted to internal communication

Hot works

Before starting the work...

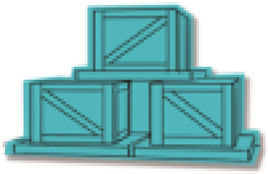
➔ Study the possibility of doing the work in the maintenance shed or in another zone specially designed to avoid fire or explosions.

➔ Visit the location and neighbouring vicinity:
Look for links with neighbouring installations (pipes, casings, gutters, false-ceilings, openings…).

Specific permit

➔ Draft a specific 1 day permit .

Yellow Tag



Combustible material

➔ Displace combustible material beyond 10 m (33ft).

Protection

➔ Protect exposed areas and block openings though which incandescent particles could pass.

➔ Cordon off the area

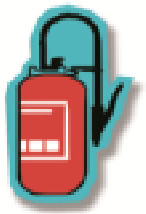
➔ Wet floor

Explosion control

➔ Take specific measures for zones with a risk of explosion

As a minimum scan explosimetre monitoring (before and during).

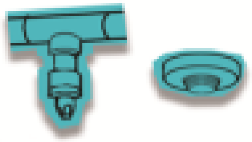
➔ ATEX areas, flammable liq tank / waste water network …..



Fire fighting

➔ Be prepared for fire fighting.

As a minimum have extinguishers at hand.



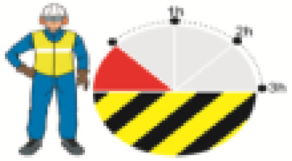
Fire systems

➔ Depending on work in progress and the difficulties encountered (false alarms) decide whether to impair

Equipment Conformity

Check the equipment (pipes, gas cylinders secured ..)

Qualified and protected operators



Post work fire watch

➔ Permanently present for 1 hour.

➔ Patrols every hour for 3 hours

Alert / Help

➔Define the means of alerting help
➔Check the work
➔In the case of a problem or unexpected event:
Stop the work, alert and call a supervisor

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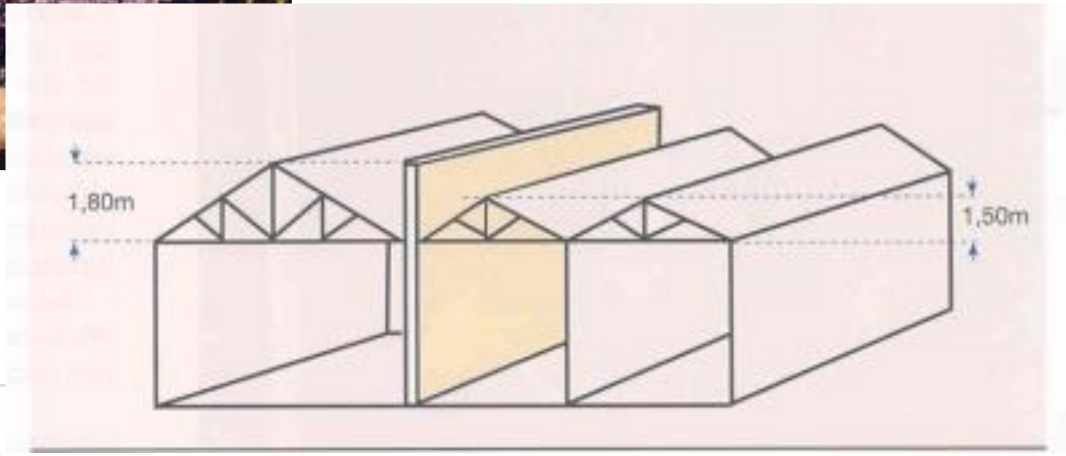
FIRE PARTIONING ASSESSMENT

- One block ?
- Many buildings/workshop ?
- Fire wall + door ?



2 x 2 hours fire doors

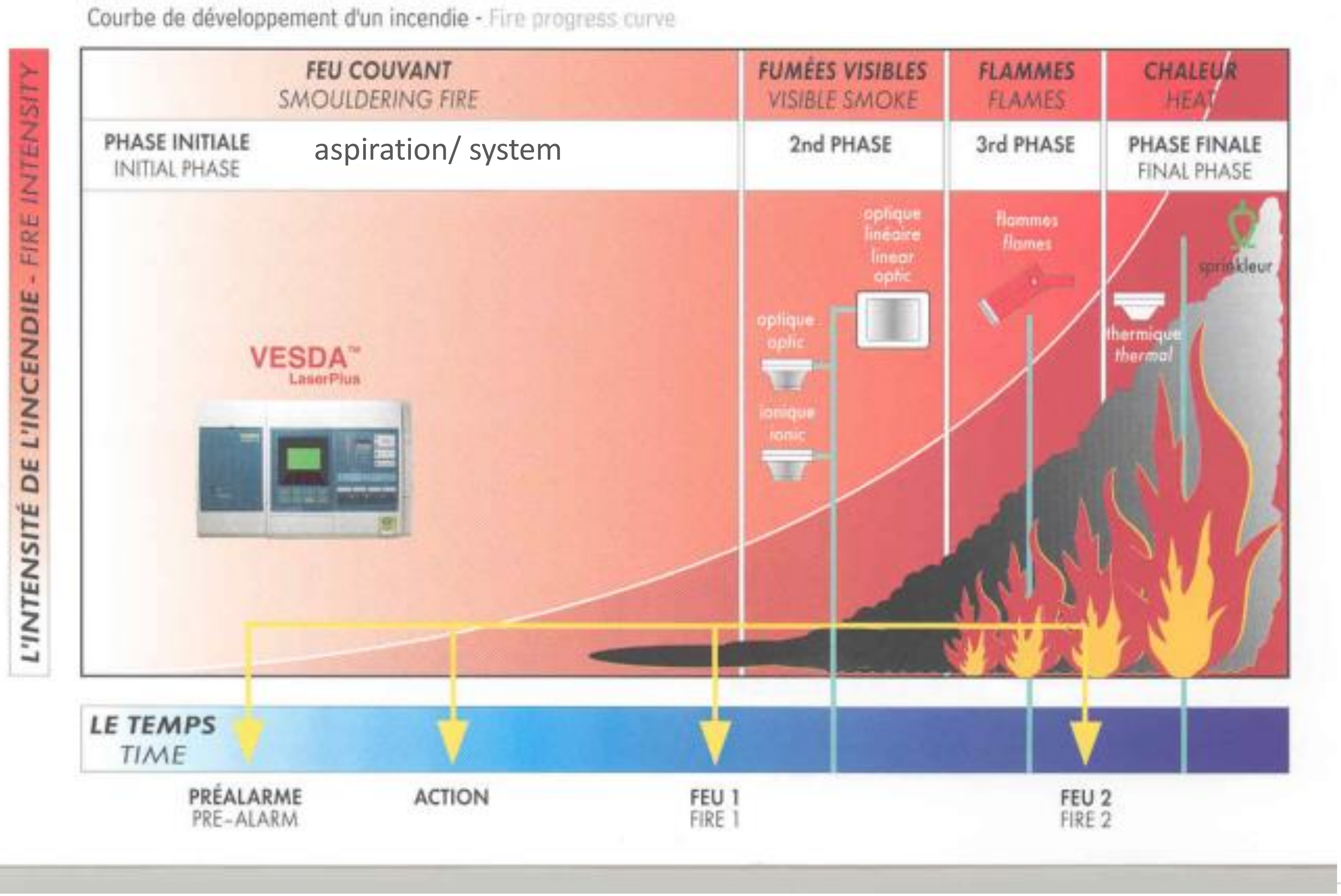
2 – SUBJECT OVERVIEW : FIRE DETECTION

Smoke removal

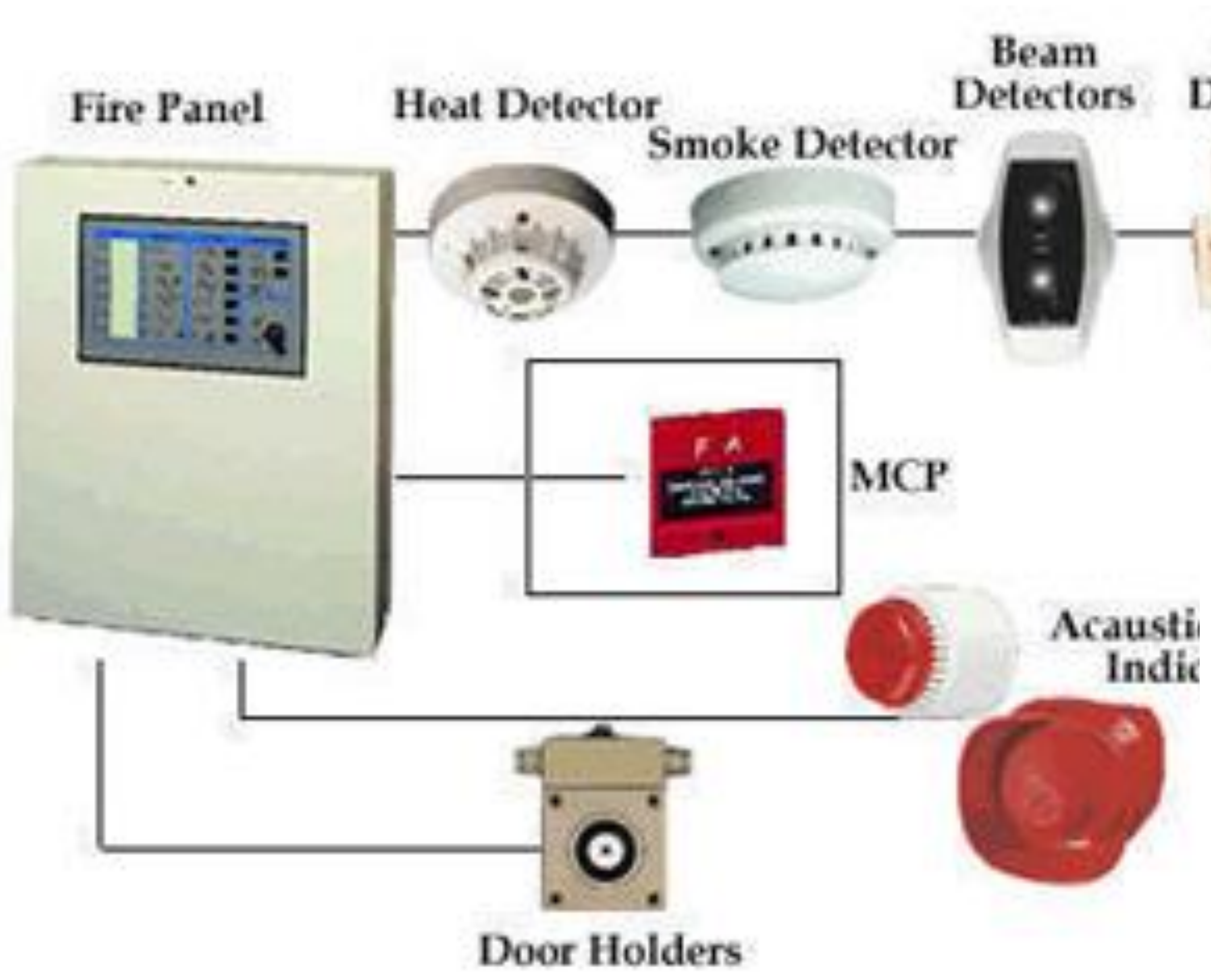
Detection

Action

2 – SUBJECT OVERVIEW : FIRE SOURCES



2 – SUBJECT OVERVIEW : FIRE DETECTION



Smoke removal

During the visit:

- is the room equiped with Fire Detection ?
- Adapted to the risk ?

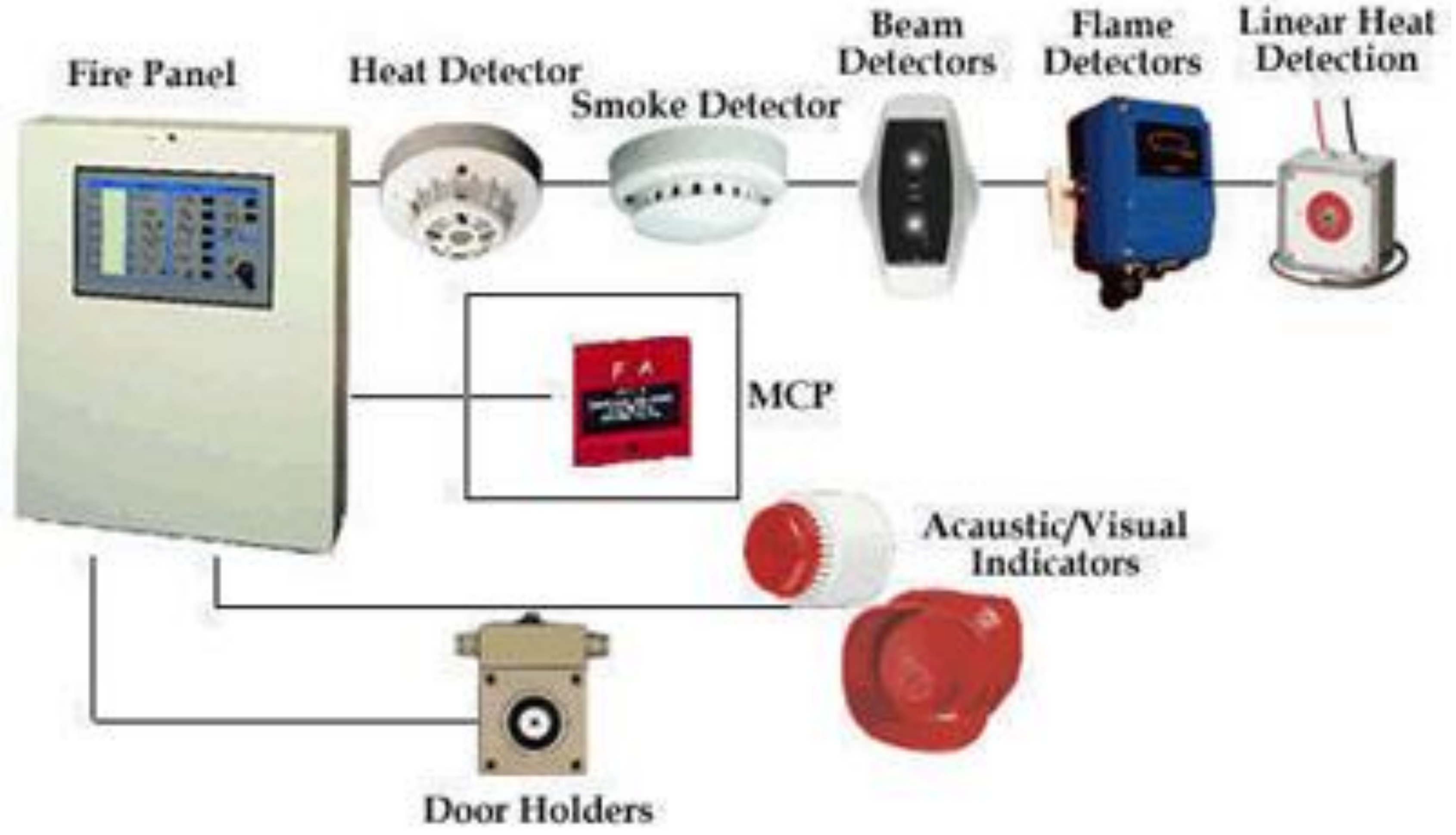
During documention review:

- Maintenance / inspection ?

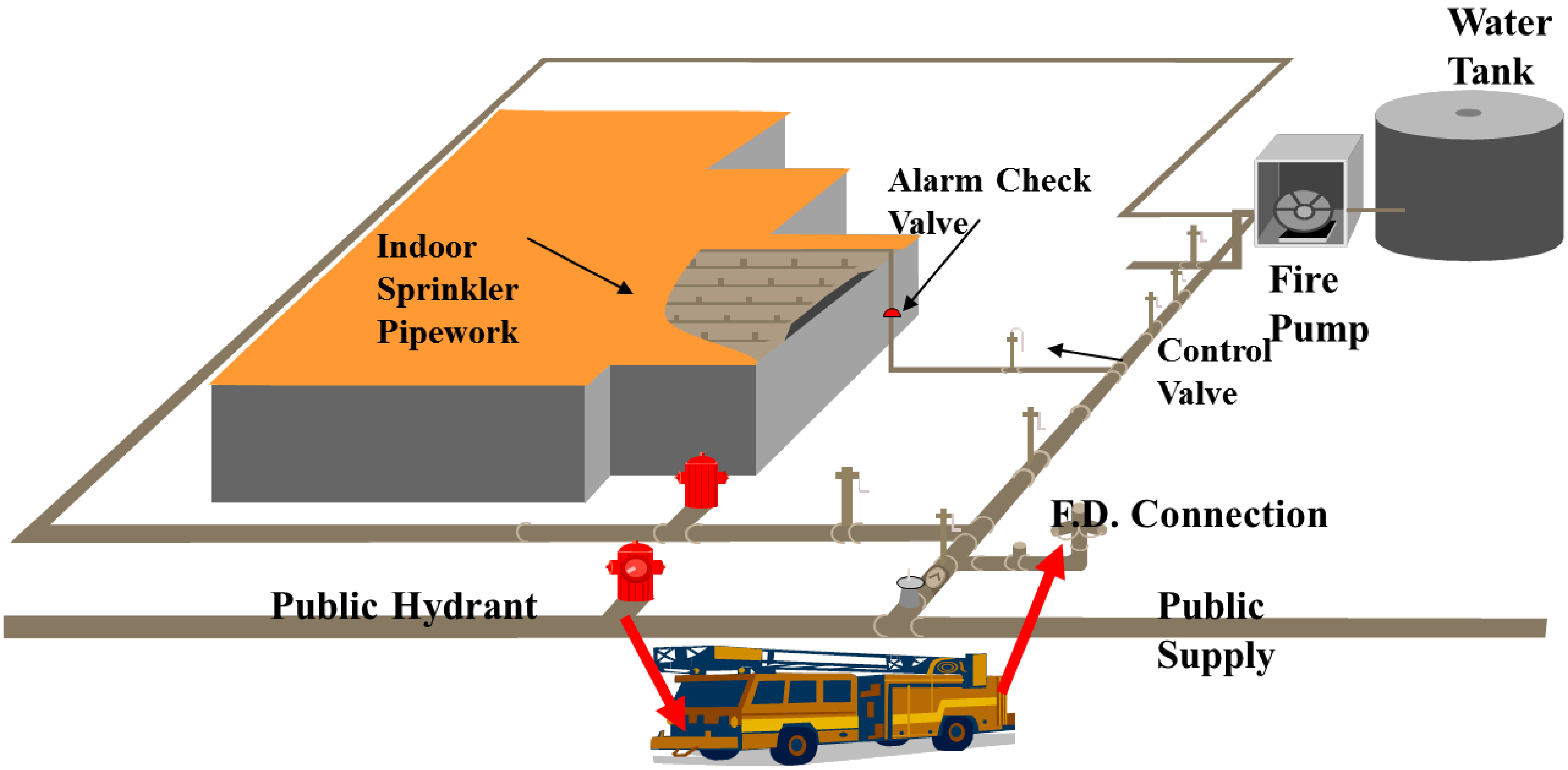
2 – SUBJECT OVERVIEW : FIRE DETECTION

24h/7 ?

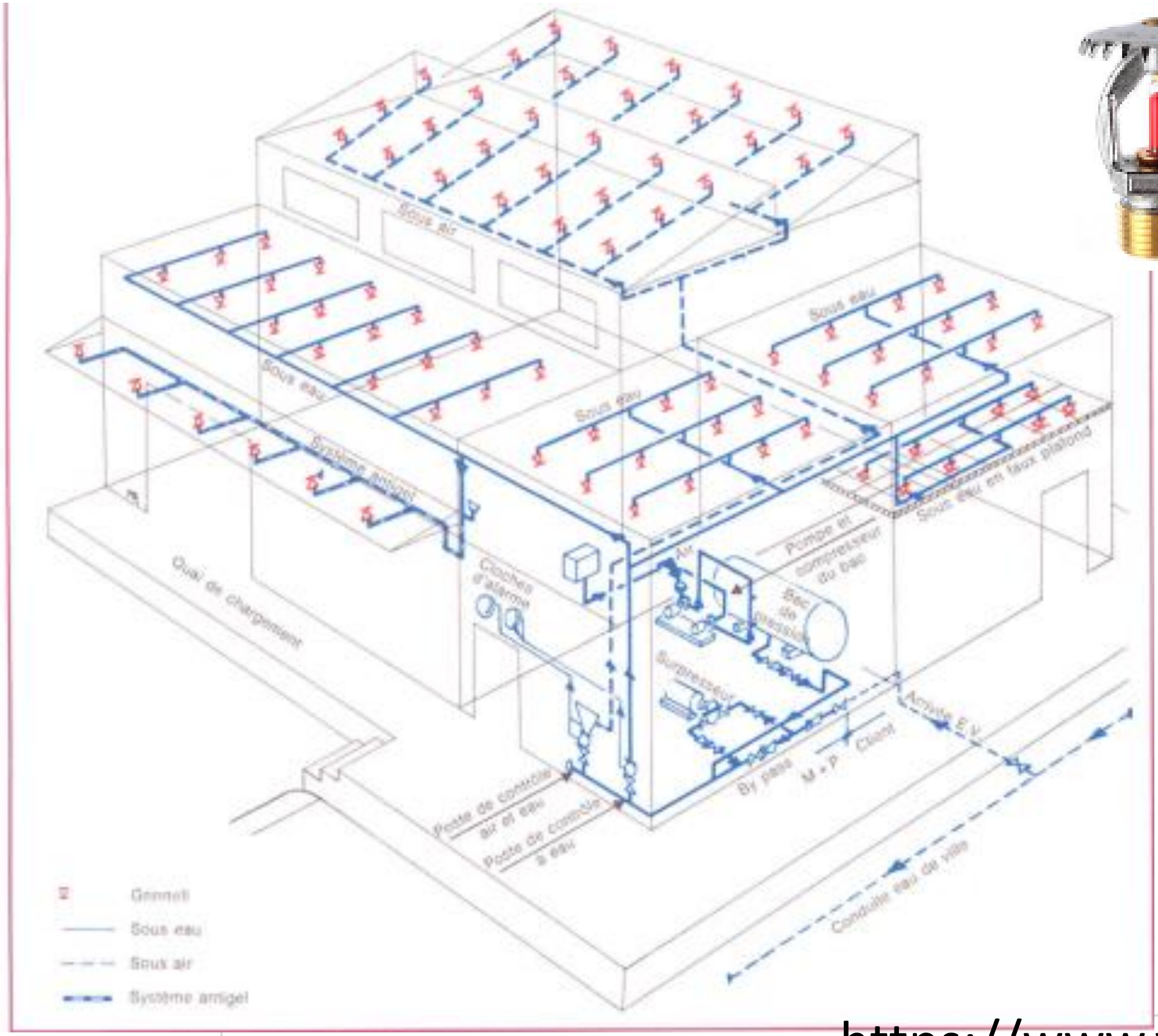
Distance to the fire brigade ?



2 – SUBJECT OVERVIEW : FIRE DETECTION



2 – SUBJECT OVERVIEW : SPINKLER Network



Extinguishing activation:

- By sprinkler network
- By dry sprinkler network
- By fire detection
- Manually (?)

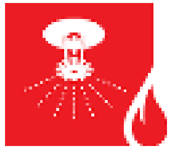
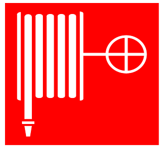
During the visit:

- Is the workshop covered by Sprinkler?
- Adapted to the risk ?

https://www.youtube.com/watch?v=o-ylvugYc0w

2 – SUBJECT OVERVIEW : SPINKLER

(Sprinkler System Demand + Hose Stream Demand) x Required Duration = Water Supply Demand

( + ) x 3 hours = 

- Total capacity ?
- Anti-freezing system ?
- Low level alarm ?

- Sprinklers: 12.2 l/min/m². over 278 m²
- Hose stream demand: 2840 l/min
- Required duration: 3 hours

EXAMPLE :

(12.2 l/min/m²) (278.8 m²) (110%) = 3741 l/min

Hose demand = 2840 l/min

3741 l/min + 2840 l/min = 6581 l/min

(6581 l/min) (60 min/hr.) (3 hrs.) = 1185 m³

2 – SUBJECT OVERVIEW : SPINKLER PUMP

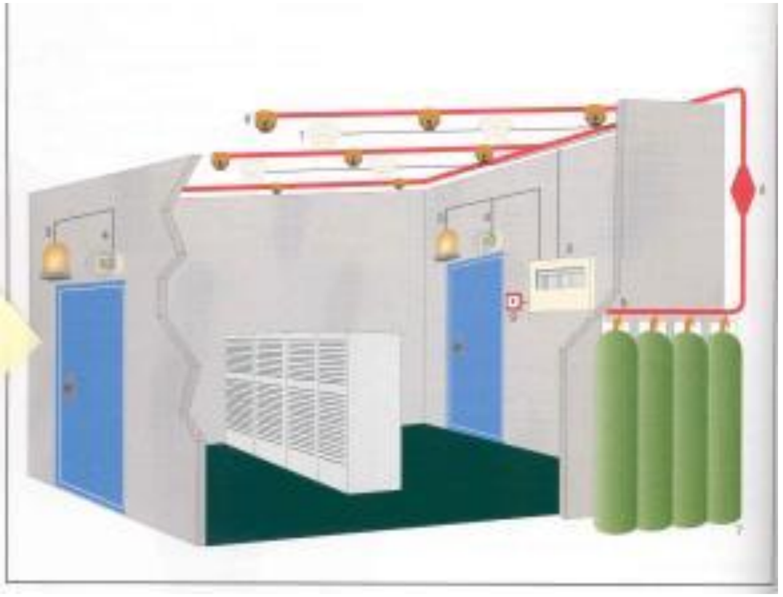
During the visit: at sprinkler pump station

- 1,2,3 pumps ?
- Diesel ? Electrical pumps ? (generator)
- Flow m3/h
- Fuel storage /Battery / Oil
- Lamps / Key of the control panel
- Safe conditions: fire proof, locked, order
- Maintenance

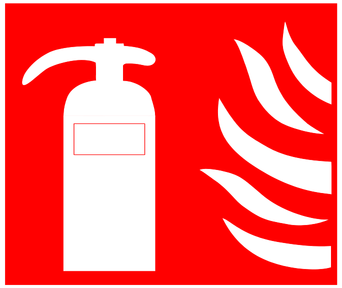
During documention review:

- Sprinkler certificat
- Maintenance / inspection

Other extinguishing systems



2 – SUBJECT OVERVIEW : Fire extinguishers



Industrial Activity

1 extinguisher 9 l of water or 9 kg of powder by 200 m2 or
1 extinguisher 6 l of water or 6 kg of powder by 150 m2 or
3 extinguisher 5 kg CO_2 by 200 m2

Additional subsidy

Localized hazard (electric cupboard, transformer, compress
generator, electric engine, special machine):
An adapted fire extinguisher has to be unless 5 m of the danger

Storage (height > 3 m)

1 extinguisher on wheel of 50 kg (water or powder) by 100 m2, from 400 m2 of storage

This *subsidy is useless on the storage witch is provided with RIA*

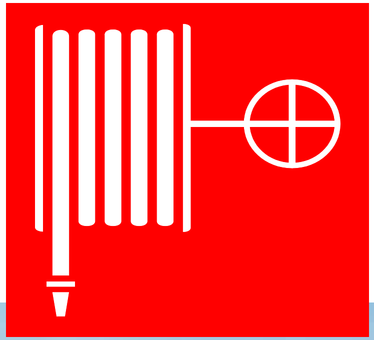
During the visit

Clear access + Labelling + check inspection label

During documentation review

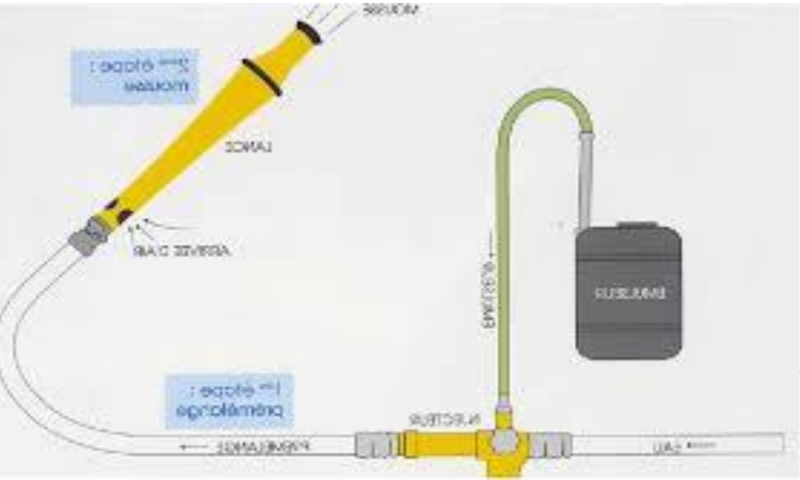
Training + inspection

2 – SUBJECT OVERVIEW : Fire reels and hose



- A specific fire hose network should supply fire fighting points with a fire reels and hose (FPHS).
- The location of the FPHS's should make it possible to sprinkle one point of the building with 2 FPHSs.

- \+ FOAM << Quantity / time limit use



<u>During the visit</u>

Clear access + Labelling + check inspection label

<u>During documentation review</u>

Training + inspection

2 – SUBJECT OVERVIEW : FIRE STRATEGY???

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What is the site fire prevention and protection strategy ??? Human/Organizational or Technical

EXAMPLES	Solution 1 (-)	Solution 2 (+)
Chemical site	Fire or gas detection and on site fire brigade	Automatic sprinkler system with foam
Chemical workshop with sodium handling	Clear sign: No water! / No connections of water pipe in the process	Gas extinguishing system / special powder
Warehouse	Fire detection and on site fire brigade Fire hoses /	Automatic sprinkler
Sterile Pharmaceutical class A	Fire detection and on site fire brigade Gas extinguihers Contamination by smoke ????	*Sprinkler with preaction ????* *Sometimes water and smoke can cause more damages ?????*
Packaging	Fire detection and on site fire brigade Fire hoses /	Automatic sprinkler
OEB5 workshop	Fire detection and on site fire brigade Gas extinguiher / Water polution	(sometimes sprinkler can create more dammages ?????)
Biological agent workshop	Fire detection and on site fire brigade Gas extinguiher / Water polution	(sometimes sprinkler can create more dammages ?????)
Technical areas (Electrical / Dust collector/Filters ….)	Fire detection and on site fire brigade Gas extinguiher	Automatic sprinkler

88	Are **emergency exits and evacuation** routes clearly marked, kept free of obstructions (unlocked)? Are emergency exit signs illuminated with emergency backup power?	Yes No Please explain: Yes No Please explain:	Yes No Comments
89	Are regular **emergency evacuation drills** conducted, and what is the frequency?	Yes No Frequency:	Yes No Comment
90	Are **emergency response** plans in place?	Yes No Please explain the key points of the emergency response plan: Indicate when the plan was last revised:	**AUDITOR GUIDANCE:** Describe if the relevant emergency scenarios been addressed in the emergency response plan - Natural: Earthquake, flood, tornado, hurricane, drought, etc. - Chemical: Spill, fire, wastewater treatment plant upset, - Human: Evacuation, first aid, medical emergency, civil unrest, active shooter/security threat, Does the facility have a communication system to alert the local community of impacts in the event of major emergency?
91	Does the site have an o**n-site emergency response team that is trained for fire or other emergencies?**	Yes No NA If yes, please explain:	Yes No NA Comments

2 – SUBJECT OVERVIEW : EVACUATION

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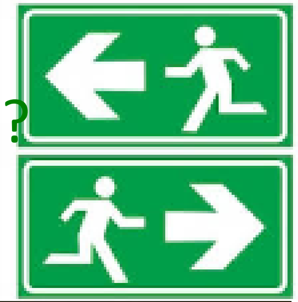
<u>During site visit: In each workshops/room:</u>

- are the evacuation ways clear and easy access?
- with emergency light?
- evacuation plan ?
- siren ?



<u>During the documentation review</u>

- Date of evacuation drill + report
- Emergency Siren/light suply power ?
- Who gives alarm?
- Training ?
- Including in emergency plan or in a SOP ?

2 – SUBJECT OVERVIEW : FIRE SOURCES

During the visit

- Equipment for Fire / Environment / Chemical Risk ….
- PPE

During documentation review :

- Number of emergency team?
- Shift 24/7/365 ?
- Distance of fire-brigade ?
- Check emergency plan : Roles and responsabilties / Alert to the authorities

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Historical data

On live data and alert network

3 – PROBLEM TOPICS: FLOOD

Prevention /Protection measures

<u>Before the flood</u>

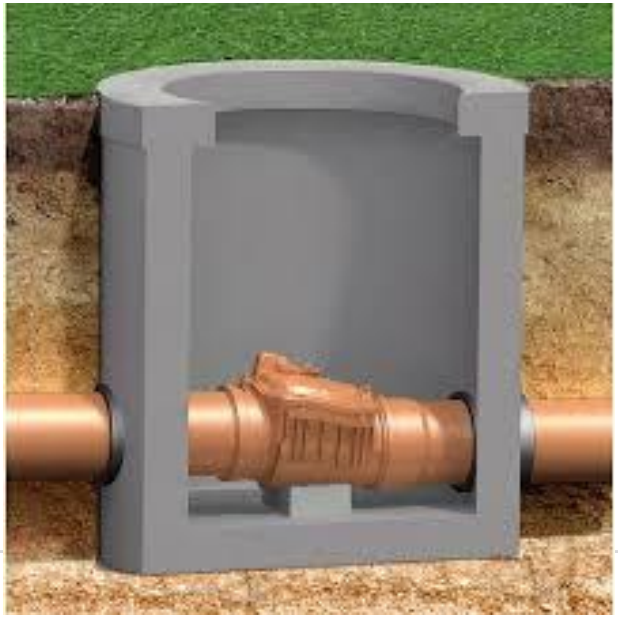
- **Evacuate the raw material/ finished product**
- **Protect equipment**
- **Anti-flooding system**

<u>During the flood</u>

- Inspection

<u>After the flood</u>

- **Pumping / Cleaning**
- **Ventilation/ Drying**



Natural Hazards

Munich Re Nathan Natural Hazard Database: Earthquake

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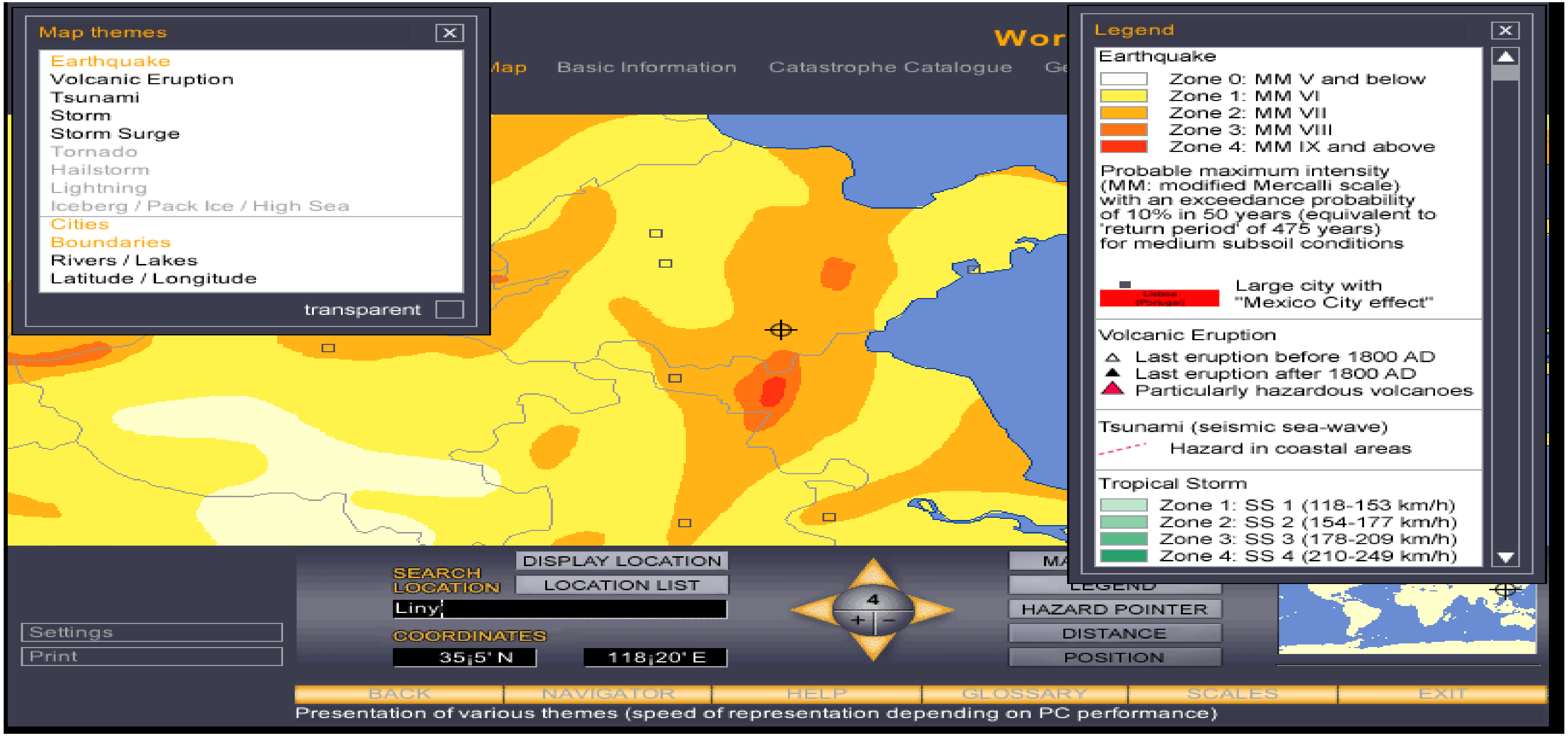

3 – PROBLEM TOPICS

- Eartquake resistant building
- Specific Storage
- Automatic seismic gas shutoff valv
- Specific sprinkler design
- Training

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2) Hazard Information

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Topic	Question summary
Hazard Information	• Safety Data Sheets (SDSs) for all hazardous substances

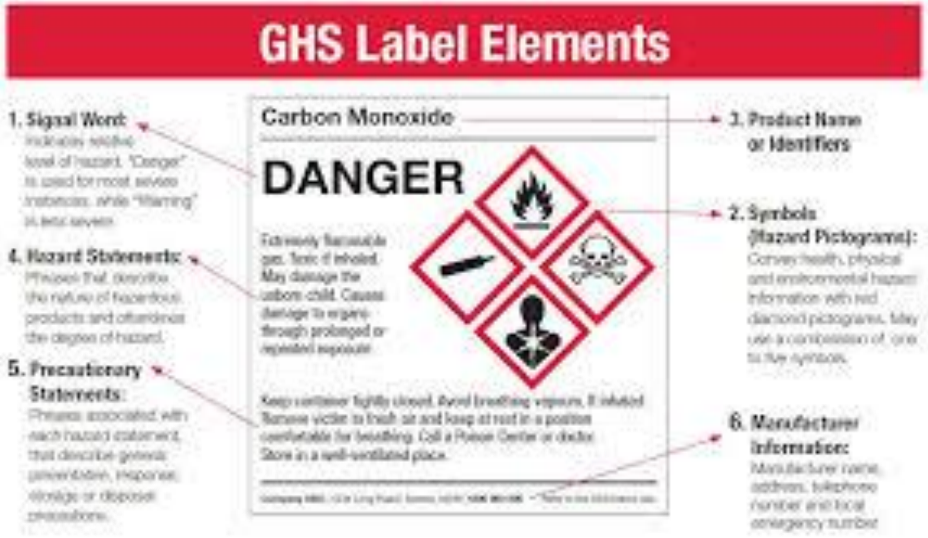
92	Does the facility maintain Safety Data Sheets (SDSs) for all hazardous substances?	Yes No Please explain:	AUDITOR GUIDANCE **WHO** edit/valid MSDS of your products ? **HOW** do you collect MSDS from your suppliers? Local **LANGUAGES** ? **ACCESS** for your operators/occu physician …? **ACCESS** for your clients ? TRAINING program covering the properties and health effects of the hazardous substances, use of and access to SDSs, container labeling and safe handling procedures?

1 – AUDIT OVERVIEW

During the site visit:

- Ask for a SDS to an operator
- Check labelling of raw, material, INTERMEDIARE, finish product

- During the documentation review:
  - WHO edit/valid SDS or labels of your products (16 chapters)?
  - HOW do you collect SDS from your suppliers?
  - Local LANGUAGES ?
  - ACCESS for your operators/occu physician …?
  - ACCESS for your clients ?
  - TRAINING program?



4 – EXAMPLE AUDIT FINDINGS

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- No exit doors in the raw material warehouse W2 and finished goods warehouse W6
- Emergency light in the workshop B56 are not available.
- There are no smoke detectors, nor sprinkler, nor permanent presence on the site. Fire water storage is not available
- All emergencies doors are not identified
- The liquid substance Trimethylchlorosilane (CAS-# 75-77-4), which is violently reacting with water under formation of massive amounts of gaseous HCl, is stored in 200 L steel drums (in total about 4-5 to) together with all other flammable liquid drums in the area W34. There is no warning signs “no extinguishing with water” .
- Emergency evacuation drill are not conducted regularly , the latest drill was conducted in September 2014 . (we were in 2018 !!)
- Emergency response team responsibilities are not defined in the emergency plan
- Occupational physician has no access to the SDS database

EXAMPLE What is wrong?

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84	Are the following areas of the facility equipped with fire detection/protection systems?	Site areas	Fire/smoke detectors	*Sprinkler or suppression* systems	Comments The site is partialy covered by sprinkler and fire detection.
		Raw material storage areas	Yes	No	Yes
		Flammable liquid storage tanks	Yes	Yes	Yes
		Process areas	Yes	Yes No	Yes
		Finished product warehouse	Yes	Yes No	Yes No
		Hazardous waste storage area	No		No

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84	Are the following areas of the facility equipped with fire detection/protection systems?	Site areas	Fire/smoke detectors	Sprinkler or suppression systems	Comments Sprinkler is designed according NFPA rules. 2 diesel pumps (350m3/h) and a sprinkler tank 500m3 The site is partialy covered by sprinkler and fire detection.
		Raw material storage areas	Yes	No	Fire detection / fire hoses at all gates of the buildings
		Flammable liquid storage tanks	Yes	Yes	Manual foam canons in place
		Process areas	Yes	Yes No	Process areas are all equiped with fire detection Worshop A B are sprinkled Whorshop C is not covered by Sprinkler
		Finished product warehouse	Yes	Yes No	There is no sprinkler in FP warehouse
		Hazardous waste storage area	No	No	No

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What is wrong ?

118	Does the site have an on-site emergency response team that is trained for fire or other emergencies?	Yes If yes, please explain: Team in place for spills.	No Comments Site leadership team provided documentation about spillage training

118	Does the site have an on-site emergency response team that is trained for fire or other emergencies?	Yes If yes, please explain: Team in place for spills.	No Comments Site leadership team provided documentation about spillage training

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What is wrong ?

120	Does the facility maintain Safety Data Sheets (SDSs) for all hazardous substances?	Yes Please explain: Training session	No Comments Site leadership team provided details and documentation for Haz Comm training to site personnel.

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What is wrong ?

120	Does the facility maintain Safety Data Sheets (SDSs) for all hazardous substances?	Yes Please explain: Training session	No Comments SDS access trough Online system. XYZ SDS are not in local langage.

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High risk work & red flags for dangerous work

Doreen Parrish, CPEA, CHMM

Head of EHS Audit

Global Environment, Health & Safety - Shire

Introduction

Traditional programs like Process Safety Management only indirectly protect employees health and life.

More people targeted programs are required !

Programs are called :

- High Risk Work Programs
- Prevention of Serious Injuries or Fatality (SIF)

Most of the requirements are legal obligation in Europe / USA

3.Work with hazardous energies

2.Confined space entry

4.Lifting operations

5.Working at height

10. Manual handling

6.High risk contractor and construction work

Agenda

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Serious Incident, Impact or Fatality - Definitions

Fatality: a case that has caused the death of one or more individuals.

Serious Injury: life-threatening / life-altering, permanent, work-related injury;

- Life-threatening: a case that requires immediate life-preserving rescue action and that, if not applied in an immediate fashion, would likely have resulted in the death of that person. (Usually requires the intervention of emergency response personnel to provide life-saving support).
  - Examples include: significant blood loss, damage to the brain or spinal cord, use of CPR or AED, chest or abdominal trauma affecting vital organs or serious burns.
- Life-altering: a case that resulted in a permanent and significant loss or use of a major body part or organ function that permanently changes or disables that person's normal life activity.
  - Examples include: significant head injuries, spinal cord injuries, paralysis, major amputations, catastrophic fractured bones, and serious burns.

SIF Approach – High Level

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- Determined the old methods were not accurate
- Treating all events equally to drive the triangle down
- Studies show ~21% of less serious events have SIF potential
- That does not mean we can ignore the lesser events but we must concentrate more closely on those with SIF Potential (the 21%).

15 SIF Categories

Mobile Equipment / Vehicles
Used in regular operation and interaction with pedestrians, structures etc.;

Confined Space Entry
As part of regular maintenance or repair being the cause of entry etc.;

Work with Hazardous Energies
Including moving or rotating machine parts, electricity, pressure, steam systems, line breaking, tasks requiring Lock-out / Tag-out procedures etc.;

Lifting Operations
Including use of cranes, fork lift trucks, lifting beams, block and tackle etc. to physically lift an object;

Working at Height
Use of scaffolds, ladders, MEWPs or fall arrest systems etc.;

High Risk Contractor & Construction Work
Such as excavations, demolitions, removal of contaminated materials etc.;

HAZMAT

Exposure to or Release of Hazardous Material
Including APIs, intermediates or other materials that can result in asphyxiation, IDLH conditions or irreversible health effects etc.;

Release of Flammable Liquids or Gases
Including the quantity of release / exposure that must be considered in research, operation or maintenance or repair etc.;

Release of an environmental pollutant
A release of any substance to air, ground or water that may be beyond set limits or which may have a detrimental effect on the environment;

Corrosive Liquid Handling
Used in regular operation, maintenance or repair activities;

Manual Handling
Involving items of considerable weight or highly repetitive movements etc.;

Significant Process Upsets or Instability
During regular operation, maintenance or repair activities;

Unexpected Maintenance
Includes plant and equipment or systems where urgent maintenance is required etc.;

NEW!

Unexpected Changes
In items of plant and equipment or processes etc.; and

Hot Work
Activities or operations that may generate sufficient heat, sparks or flame to cause a fire Includes welding,flame cutting, soldering, brazing, grinding and other equipment incorporating a flame.

Agenda

1 **What is SIF**

2 **Confined Space Entry** (CSE)
Working at Heights (WAH)

3 Short Case Study

4 **Working with Hazardous Energies** (WWHE)
Lifting Operations

5 Short Case Study

6 **High Risk Contractors**

Short Case Study

Worker Protection			
55	Does the facility have a safe work permit system for the following?	Hot Work: Yes No NA Confined Space Work: Yes No NA Energy Isolation or Lock Out/Tag Out: Yes No NA Line Breaking: Yes No NA Work at Height: Yes No NA General Permit Yes No NA Other: Yes No Please describe:	Yes No Comments **AUDITOR GUIDANCE:** Provide the procedure title or # as reference and comment on the applicability at the site.

Confined Space Entry

This is an operation that takes often place although common thinking is that it's only related to entering in small vessels.

Typical activities :

- Manual charging of reactors
- Visual inspection
- Cleaning of equipment
- Inspection and maintenance

Confined Space Entry - Risks

- Asphyxing atmosphere
- Moving parts
  (hazardous energies)
- Exposure to chemicals
- Injuries / accident
- Difficulties during rescue

Confined Space Entry - Criteria

- No harmonized definition between companies, authorities, experts
- Usually related to a dimension (volume, length), difficulty of access, potential hazardous atmosphere / energies present
- Need to make sense, be consistent with other programs
- Need to be enforced !

Confined Space Entry – Program Elements

- Definition of Confined Space
- Inventory of Confined Space
- Permit system
- Atmosphere monitoring
- Planning of rescue operations
- Maintenance of equipment (oxygen monitoring, rescue equipment,...)

Work at heights

- All operations that are above ground ; where a fall is possible.
- Access to remote places (inspections, reparations, cleaning, maintenance)
- Access to roofs
- Access to underground or excavated areas

Work at heights - Risks

- Fall
- Fall of objects
- Impact due to moving parts (scissor lift, MEWP)
- Failure of equipment (Lack of maintenance of the ladder, platform,...)

Work at heights - Criteria

- Definition of height
  - 0 meter
  - 1.8 – 2 meters

Mobile Elevated Work Platform (MEWP)

Scissor lift

Work at heights – Program Elements

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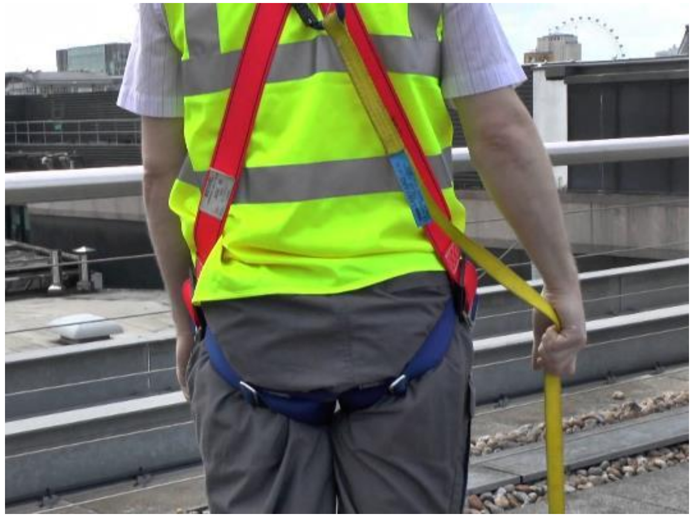
- Definition
- Risk assessment
- PPE – Fall protection system
- Rescue
- Permit system
- Maintenance program
- Safety perimeter during operation



Agenda

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Building responsible supply chains

1. SIF
2. Confined Space Entry (CSE)
   Working at Heights (WAH)
3. **Short Case Study**
4. Working with Hazardous Energies (WWHE)
   Lifting Operations
   Manual Handling
5. Short Case Study
6. High Risk Contractors
7. Short Case Study

Working at Heights

- What is right ?
- What is wrong ?

- What are doing when
you see such a situation during the audit ?

- Which documents are you checking after the visit ?

- What will be the finding(s) ?

Confined Space Entry

- What is right ?
- What is wrong ?
- What are doing when you see such a situation during the audit ?
- Which documents are you checking after the visit ?
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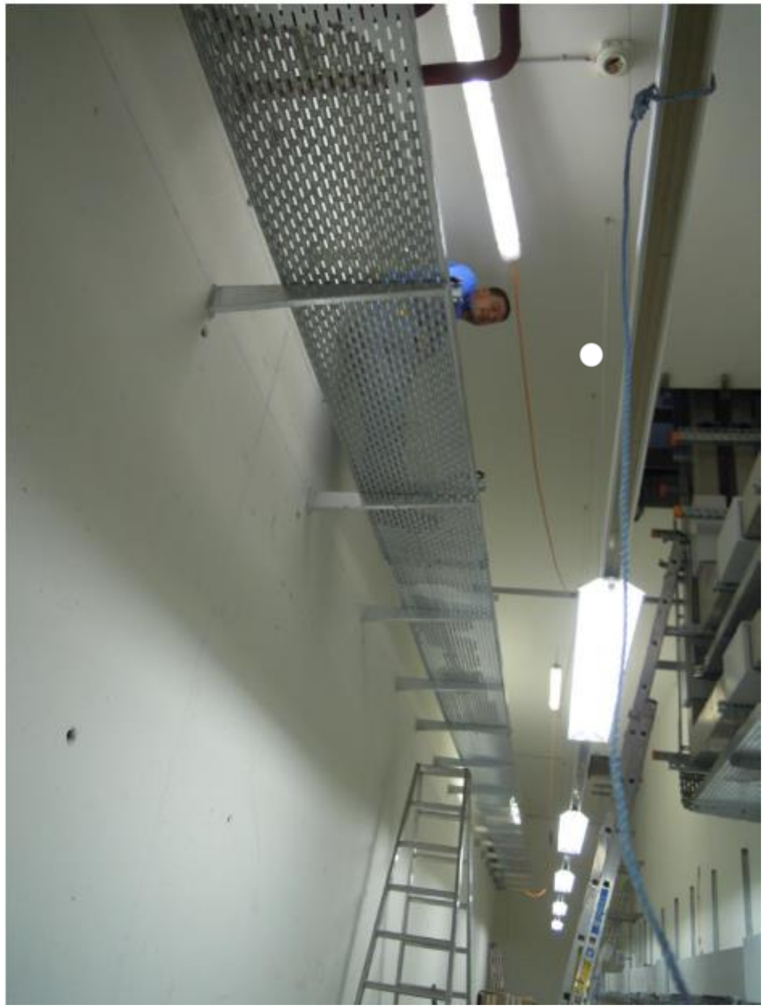
Challenging situation

During your visit, no operation like entry in a Confined Space Entry or Working at Heights take place...

What do you do to get an idea of the efficiency of their programs?

Some wrong behaviors...



Agenda

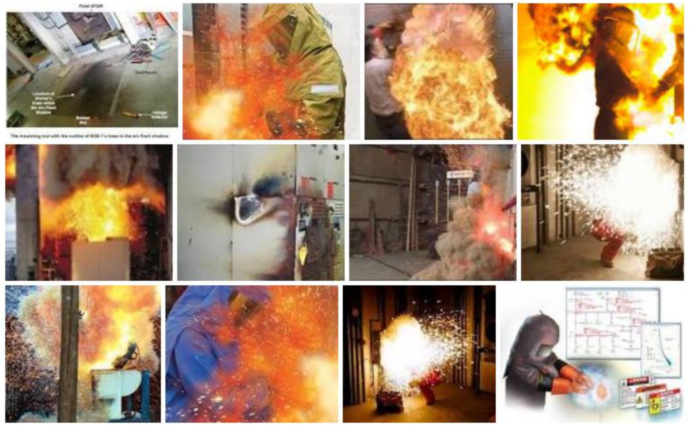
1	SIF
2	Confined Space Entry (CSE) Working at Heights (WAH)
3	Short Case Study
4	**Working with Hazardous Energies** (WWHE) **Lifting Operations**
5	Short Case Study
6	High Risk Contractors
7	Short Case Study

Worker Protection			
55	Does the facility have a safe work permit system for the following?	Hot Work: Yes No NA Confined Space Work: Yes No NA Energy Isolation or Lock Out/Tag Out: Yes No NA Line Breaking: Yes No NA Work at Height: Yes No NA General Permit Yes No NA Other: Yes No Please describe:	Yes No Comments **AUDITOR GUIDANCE:** Provide the procedure title or # as reference and comment on the applicability at the site.
56	Has the facility developed and implemented an Electrical Safety Program that includes:	Installation of lockable disconnects interlocks, and emergency stop devices? Yes No Labeling of switches, outlets, breakers, panels, and disconnects? Yes No Designating keep clear areas around electrical equipment for safe work practices? Yes No Electrical cabinets are locked? Yes No Arc Flash Analysis? Yes No	Yes No Comments
57	Has the facility developed and implemented machine guarding procedures (including conveyor systems or other overhead equipment conveying materials (side rails, netting, etc.)) with proper hazard symbols?	Yes No NA Comments:	Yes No NA Comments

Working with Hazardous Energies - Sources

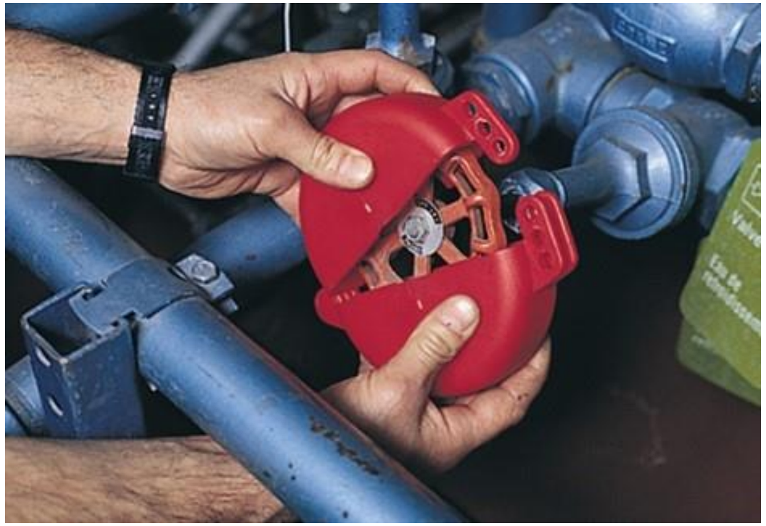
Hazardous energies sources include electrical, mechanical, hydraulic, pneumatic, chemical, thermal, or other sources in machines and equipment can be hazardous to workers.

- Moving or rotating machine parts (Mechanical)
- Pressure or steam systems
- Hazardous materials
  (e.g., chemicals, solvents, toxic gases, asphyxiants gases etc.)
- Gravity & stored energy
  (e.g., springs, potential energy which would cause equipment to move or rotate, explosion suppression systems, etc.)
- Electricity
  (mains and stored e.g., capacitors)
- Pneumatic valves
- Extreme temperatures
- Ionizing and non-ionizing energy sources
  (e.g., nuclear, x-ray, lasers, UV, etc.)



Program Elements

- Definition
- Permit system
- Lock-out tools
- Tag-out tools
- Procedure for special cases
- Possibility of locking out
  (can be checked during visit also if there is no LOTO currently taking place)



Working with hazardous Energies

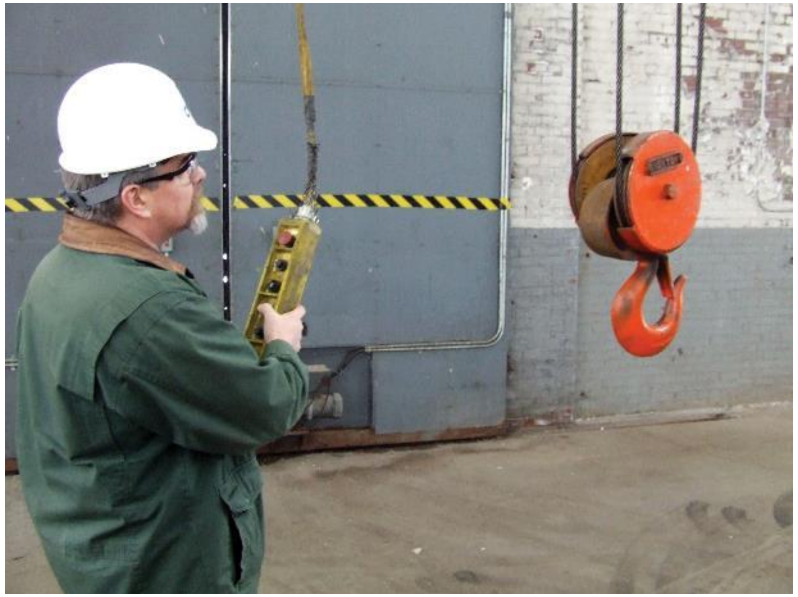
- Any work done on an equipment that can release energy and harm people
- Working on a packaging line that is switched on by someone else
- Retained energy like compressed air, spring...
- Work on electrical equipment

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

59	Are the facility's pedestrian and material handling equipment aisles marked or designated?	Yes No Please explain:	Yes No Comments
60	Has the facility developed and implemented a formal program to provide for the selection and maintenance of Material Handling Equipment?	Yes No Does it include: Operation by trained persons? Yes No Periodic inspection and preventive maintenance by qualified personnel? Yes No If elevated work devices are used is appropriate fall protection equipment in place and is a rescue plan in place? Yes No Please explain:	Yes No Comments
61	Are the facility receiving and/or shipping docks equipped with wheel chocks, dock locking systems or other means of trailer restraint to prevent trailers from moving during loading/unloading?	Yes No Please explain:	Yes No Comments
62	Is product stored overhead in pallet racking stretch wrapped or secured by some means to prevent it from falling?	Yes No Please explain:	Yes No Comments
63	Does the facility have practices to ensure pallet racking is maintained in good condition and regularly inspected (no obvious damages to components – especially uprights – cross beams locked in place, foot plates secured to floor, and capacity posted)?	Yes No Please explain:	Yes No Comments

Lifting Operations

- Moving goods and materials using dedicated equipment
- Lifting of equipment for maintenance or repairs



Lifting Operations - Risks

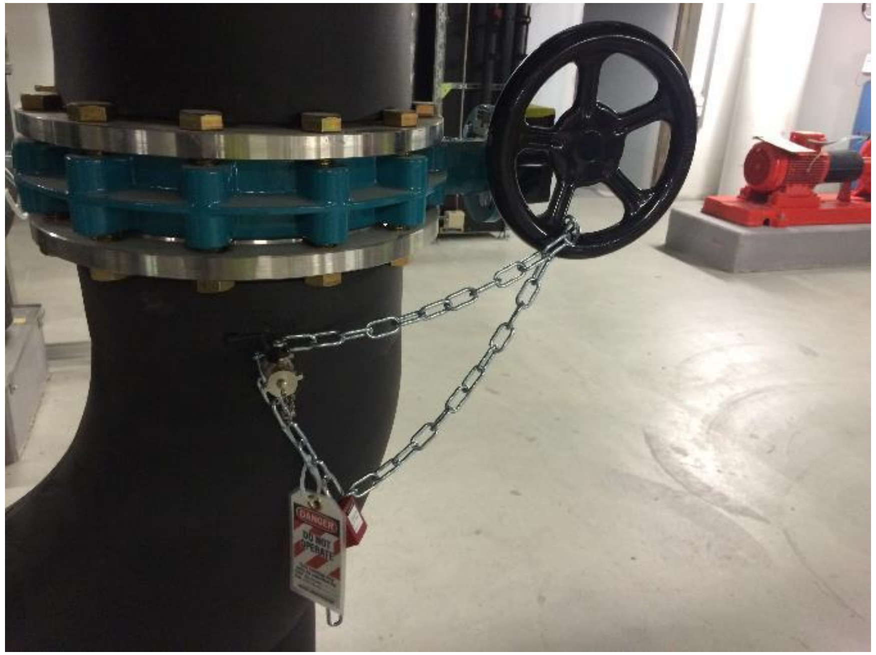
- Fall of transported goods
- Failure of lifting equipment
- Injury of persons nearby
- Damage to nearby installation (→ chain reaction)

Lifting Operations– Program Elements

- Task assessment
- Equipment clearly and visibly labeled with appropriate information
- Inspection of the equipment prior to use
- Respect of limitations
- Maintenance program

Agenda

Is this a proper Lock-out ?



Agenda

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
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PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
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58	Does the facility use any of the following processes for managing risks related to contractor activity onsite?	Contractor pre-approval: Yes No Training/orientation before entry: Yes No Electronic access control: Yes No Drug/alcohol testing: Yes No On-going recurrent safety training: Yes No Mandatory accident reporting: Yes No Other: Yes No If yes, please describe:	Yes No Comments AUDITOR GUIDNACE: Describe how you reviewed each program including details during tour, interviews and document review.

High Risk Contractors - Purpose

- Works that are not routine (= complex and high risk) are usually realised by specialised, external companies
- Includes Construction workers
- Trend in Europe/USA to have also routine work being done by external companies

High Risk Contractors - Risks

- Activity in itself
- Contractors lacking training / experience
- Not familiar with the facility
- Discrepancy between industry and «local» way of working
- Impact on adjacent / remote operations

High Risk Contractors - Criteria

Contractors performing high risk activities → definition, see ex. SIF activities

Resident contractors vs. one time contractors

High Risk Contractors – Program Elements

- Pre-selection of contractors
- On-boarding orientation (know the site)
- Need to use the Permit to Work system
- PPE / approved tools
- Checks during works
- Assessment of performance

Agenda

Short Case Study

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- What is wrong ?
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Short Case Study

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Short Case Study

Besides usual risks of getting injured (trips, falls...) :

Important fire load

Programs

When you review those programs...

- Make sure that the program makes sense
- Make sure that what is written in a SOP is implemented
- Look for proofs of efficiency of those programs
- Look for consistency of those programs
- Look for interdependency

Conclusion

Those High Risk Work or SIF Programs are very important.

They might be seen as low priority because they impact only one person at a time...

but those operations takes place several time a day therefore ***they make a difference*** !

<table>
<tr><th colspan="6">HEALTH & SAFETY COMPLIANCE AND RISK MANAGEMENT Self-Assessment Questionnaire</th><th>Auditor Verification
Please provide observations, details, comments and any supporting documents</th></tr>
<tr><td colspan="6">General</td><td></td></tr>
<tr><td>47</td><td>Does the facility have a written Health & Safety policy, procedures, and practices?</td><td colspan="4">Policy: Yes ☐ No ☐
Procedures: Yes ☐ No ☐
If yes, provide a copy of the policy and list the procedure titles:</td><td>Yes ☐ No ☐
Comments

Link or policy provided: Yes ☐ No ☐
List of procedures provided: Yes ☐ No ☐</td></tr>
<tr><td>48</td><td>Does the facility have any documented Health & Safety objectives and targets or goals for performance improvement, including metrics?</td><td colspan="4">Yes ☐ No ☐
Please describe:</td><td>Yes ☐ No ☐
Comments</td></tr>
<tr><td rowspan="6">49</td><td rowspan="6">Indicate the number of significant Health & Safety incidents that occurred at this facility over the past three years?
(Significant incidents are defined as: causing serious injuries or fatalities; a fire resulting in damage to process equipment, building, storage areas; physical explosions, fines or violations.)

If any of these incidents were or are not being tracked, please indicate this by adding “not tracked” to the appropriate cell</td><td></td><td>Three years ago</td><td>Two years ago</td><td>Last year</td><td rowspan="6">Yes ☐ No ☐
Comments

AUDITOR GUIDANCE: Please note that deficiencies in this question do not necessarily result in a finding.</td></tr>
<tr><td>Serious injuries</td><td></td><td></td><td></td></tr>
<tr><td>Fatalities</td><td></td><td></td><td></td></tr>
<tr><td>Fire</td><td></td><td></td><td></td></tr>
<tr><td>Explosions</td><td></td><td></td><td></td></tr>
<tr><td>Fines or violations</td><td></td><td></td><td></td></tr>
<tr><td>50</td><td>Does the facility provide HSE (Health, Safety & Environment) training to employees (full-time, temporary, or contractor)?</td><td colspan="4">New employee orientation and HSE training: Yes ☐ No ☐
Periodic refresher training: Yes ☐ No ☐
Pre-start up process specific HSE training: Yes ☐ No ☐
Employee emergency response action training: Yes ☐ No ☐
Hazard Communication, Yes ☐ No ☐
Process Safety Management, Yes ☐ No ☐
Environmental Practices: Yes ☐ No ☐
Comments:</td><td>Yes ☐ No ☐
Comments

AUDITOR GUIDANCE:
Review qualification for persons managing API emissions (i.e. knowledge of regulatory requirements and quantification of APIs in treated waste water)

Review the business area’s written qualifications for persons performing and reviewing environmental calculations and sampling. Ensure that the qualifications address knowledge of the process and applicable regulatory requirements.

Are employees responsible for active ingredient wastewater control practices provided suitable and sufficient information, instruction and training to be able to understand the hazards associated with environmental releases of those active ingredients and isolated intermediates?</td></tr>
</table>

51	Does the site have a program for improving safe behaviors?	Yes ☐ No ☐ If yes, please describe:	Yes ☐ No ☐ Comments
52	Does the facility ensure the provision of safe and potable drinking water and hygienic facilities to all employees?	Yes ☐ No ☐ Please explain:	Yes ☐ No ☐ Comments **AUDITOR GUIDANCE:** Water systems that could be impacted by contamination are tested for compounds of concern.
53	Does the company provide adequate sanitary facilities (e.g. clean toilets, possibilities for hand-washing).	Yes ☐ No ☐ Please explain:	Yes ☐ No ☐ Comments
54	If living accommodation (e.g. dormitories) are provided to employees or contractors, are they safe and clean, and do they meet the relevant basic requirements (e.g. fire protection and emergency)?	Yes ☐ No ☐ Please explain: If housing is provided, who has responsibility for maintenance and general HSE? Please explain: Is it ensured that housing for workers and families is not in the vicinity of production areas or with uncontrolled access to operational facility? Yes ☐ No ☐	Yes ☐ No ☐ Comments