PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Building responsible supply chains

Pharmaceuticals in the Environment

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GSK

AGENDA

Pharmaceuticals in the Environment

Introduction

Risk assessment

PSCI tool

Mitigation strategy & example

Bio

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EHS&S Lead -Third Party, GSK

- Over 20 years multi-national pharmaceutical experience, covering whole site life cycle, from Green field site location selection & construction to site transition/close.
- Experienced for various roles, including mechanical engineer, Production Supervisor, Industry Facilitator, Project Regulatory Manager, Site Risk Champion, Site Transition Manager, Production Operation manager and Value Stream Head, EHS Manager and China Region EHS Lead
- Certified Safety Engineer. Mechanical & Electrical Bachelor degree. Quality management Master degree. Six-Sigma blackbelt

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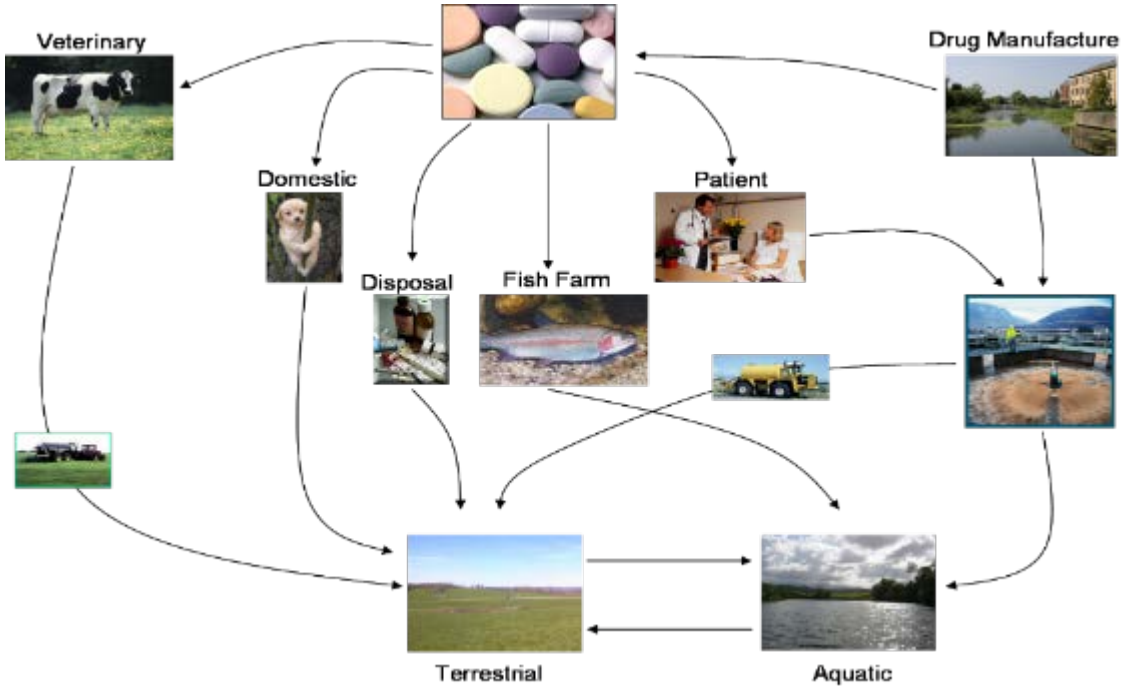
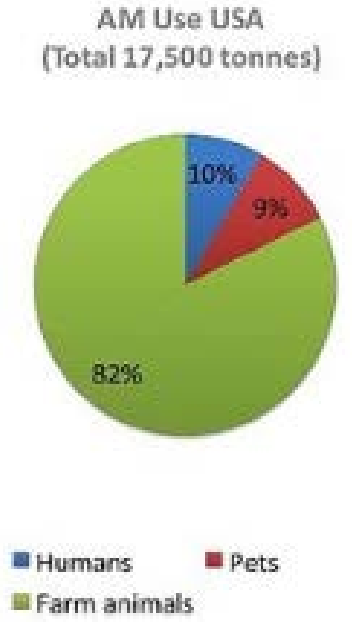
PIE Introduction

Sources of Pharmaceuticals in Surface Waters



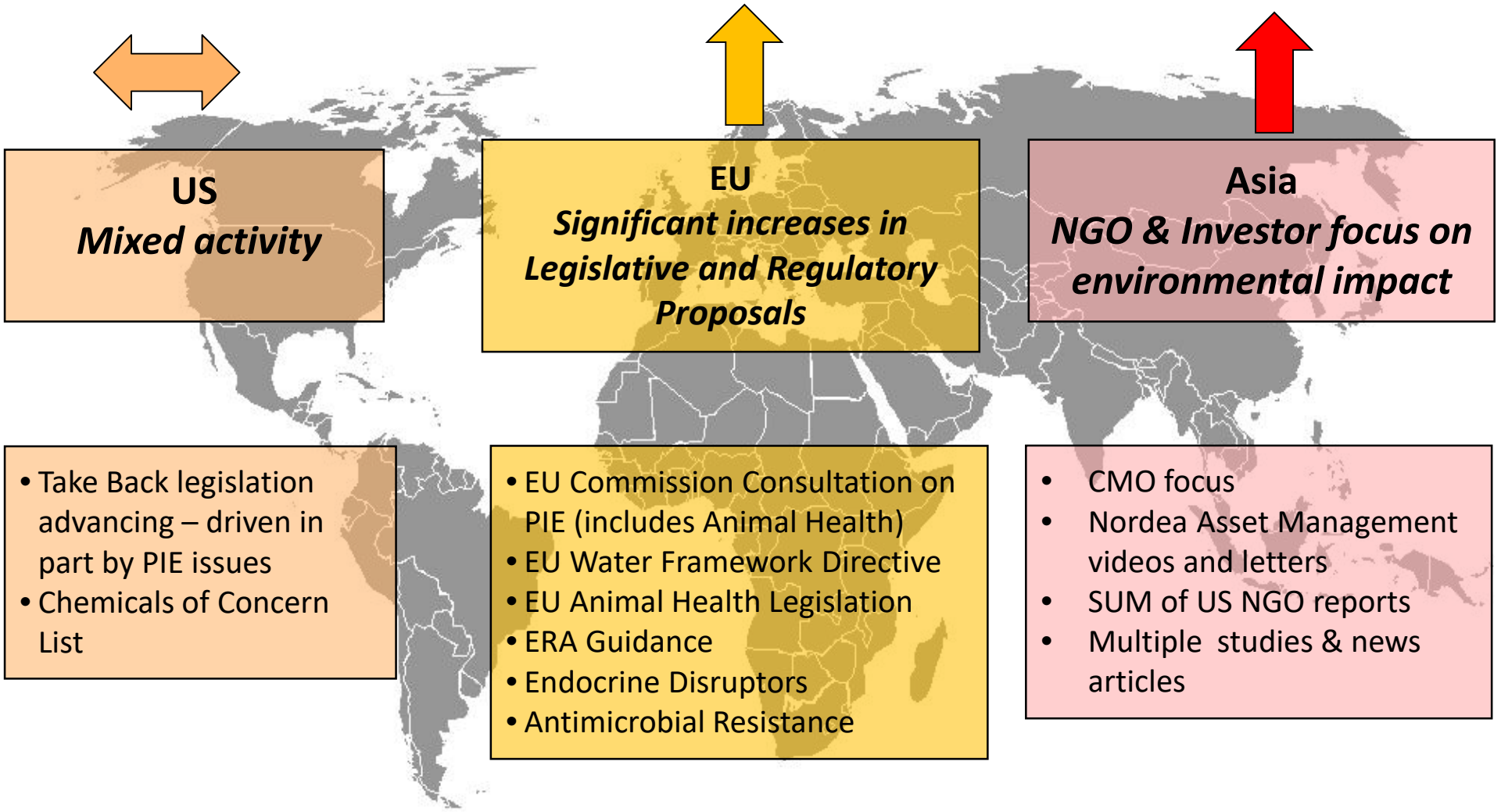


- Largest use of antibiotics globally is in animal production and human health. This is the largest source (98%) of antibiotics in the environment

- Manufacturing emissions to the environment are estimated <2% by mass.

HOWEVER this is a high profile area for pressure groups, media, NGOs etc

Global Perspective



US
Mixed activity

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

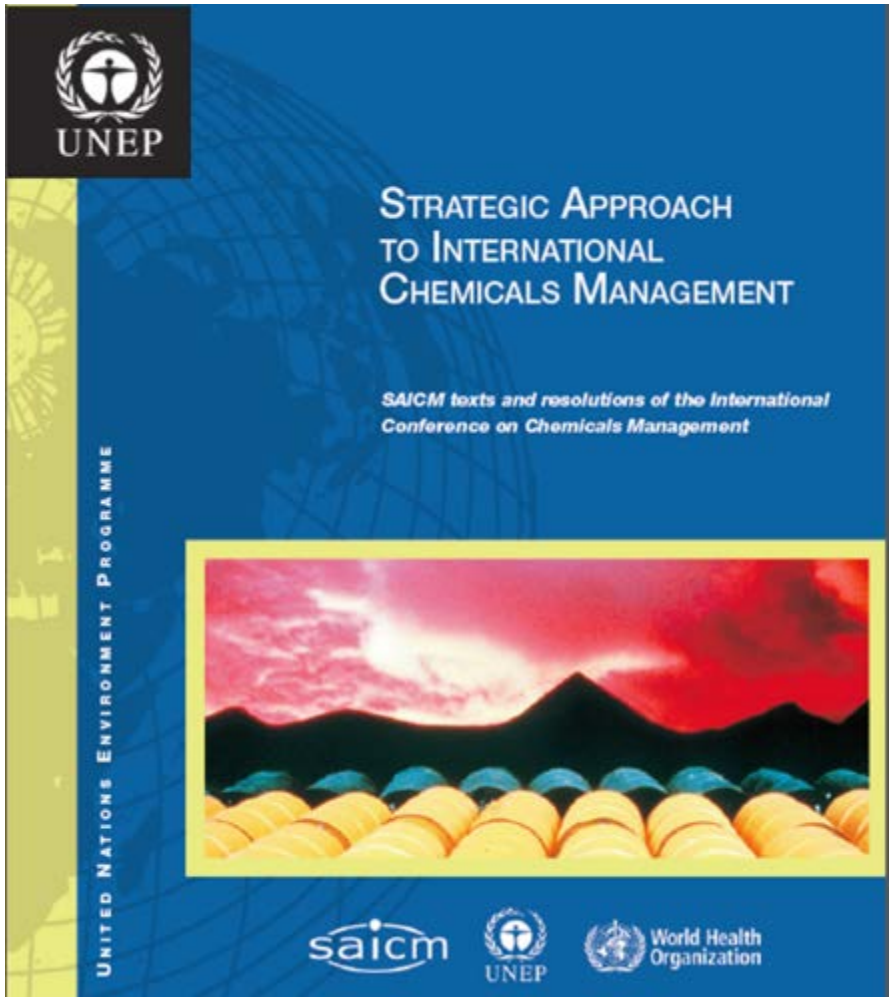
EU
Significant increases in Legislative and Regulatory Proposals

- 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*

- 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

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

World Health Organization

GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE

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)

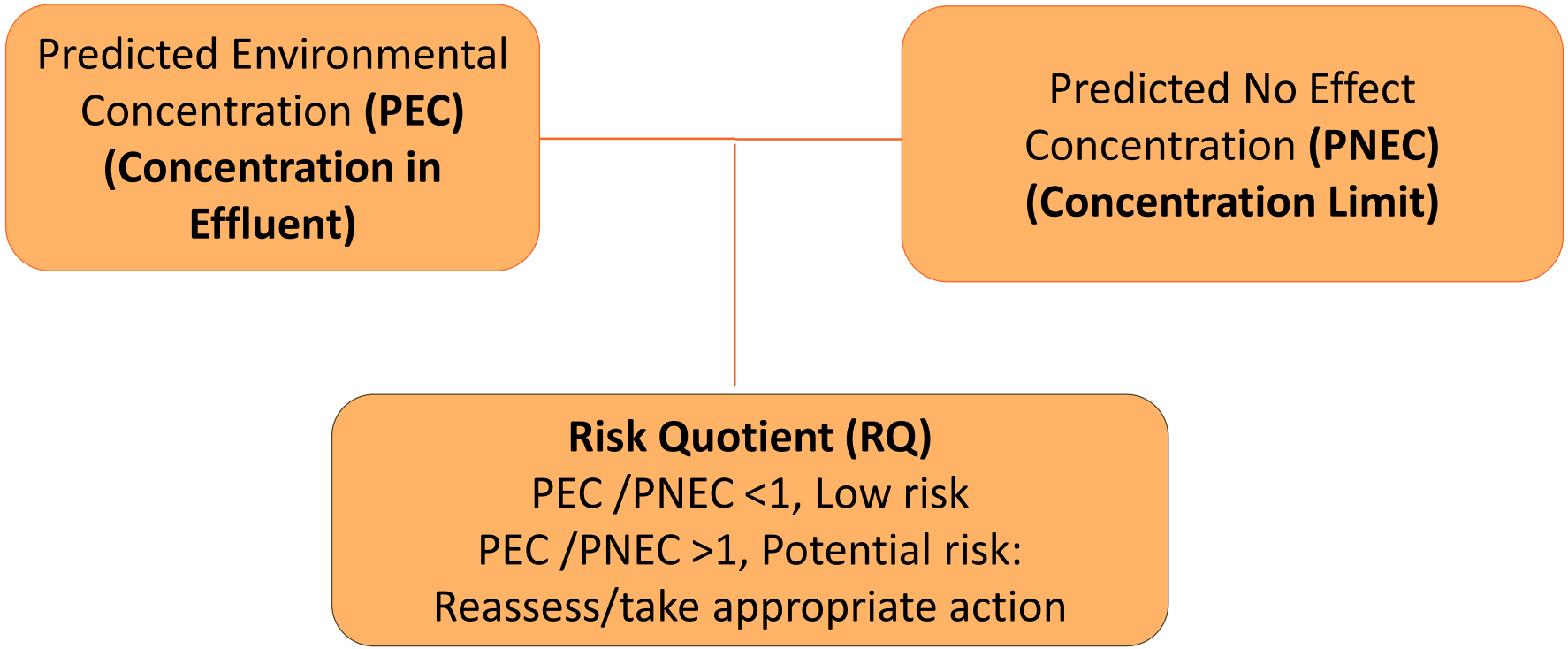
PIE Risk assessment

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



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

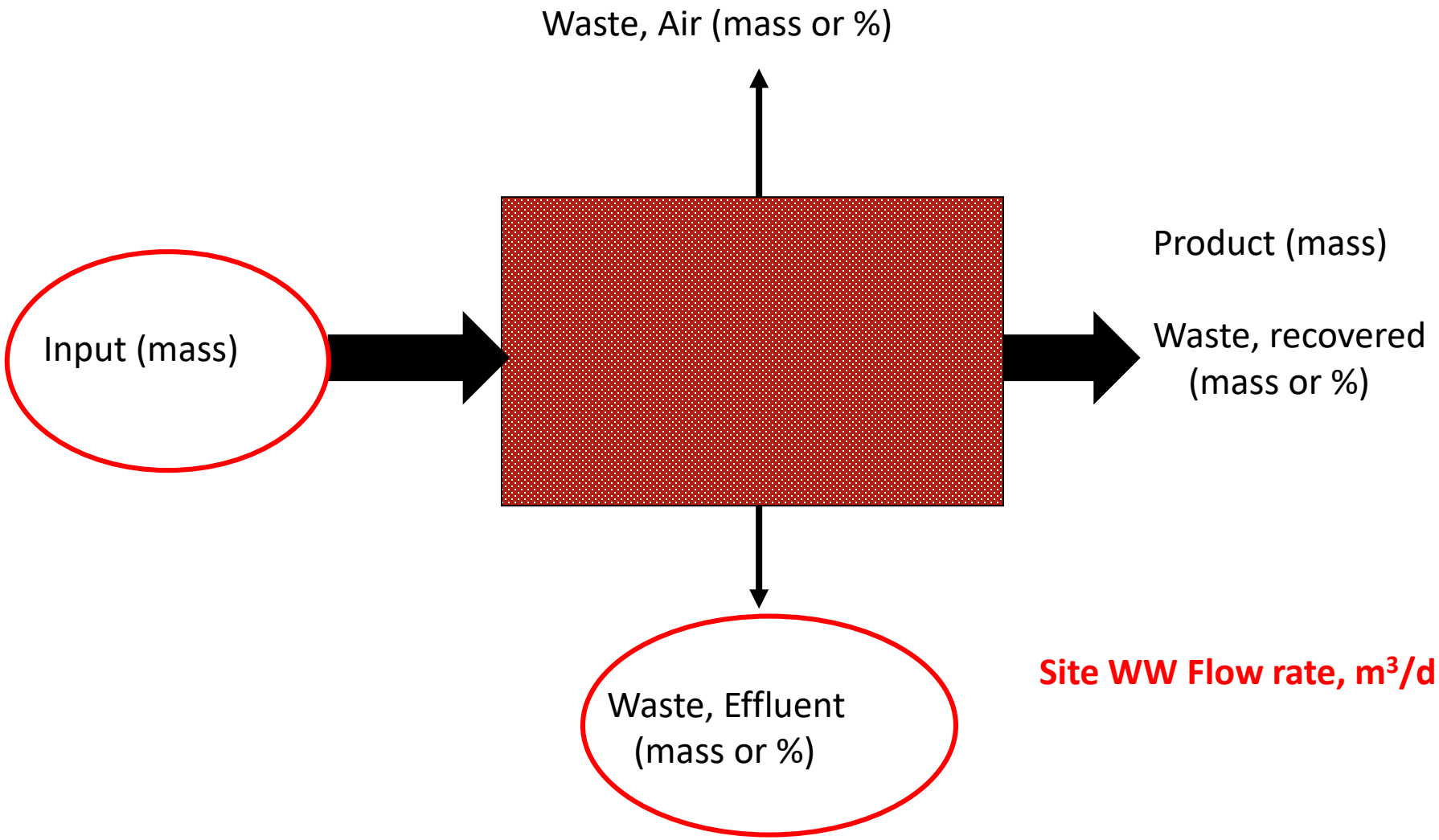
batch records	wastewater POG[1]
product yield	wastewater flows
batch/year	WWTP unit ops
cleaning cycles	API analyses[2]

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



API Mass Balance Loss - Example

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

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

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	

Permits

- 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 NOT directly address active pharmaceutical ingredients (APIs) but DO include a 'general duty' clause, i.e., "No toxics in toxic amounts".

Guidance

SETAC PRESS

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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

PSCI tool

Audit Overview | Wastewater question

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 | Auditor guidance for wastewater

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.

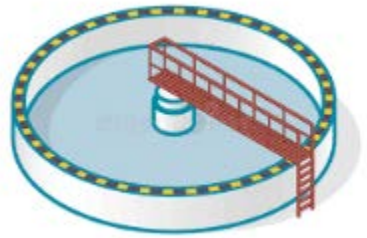
Review qualification for persons managing API emissions (i.e. knowledge of regulatory requirements and quantification of APIs in treated waste water)

PIE mitigation Strategy & Examples

Strategy

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

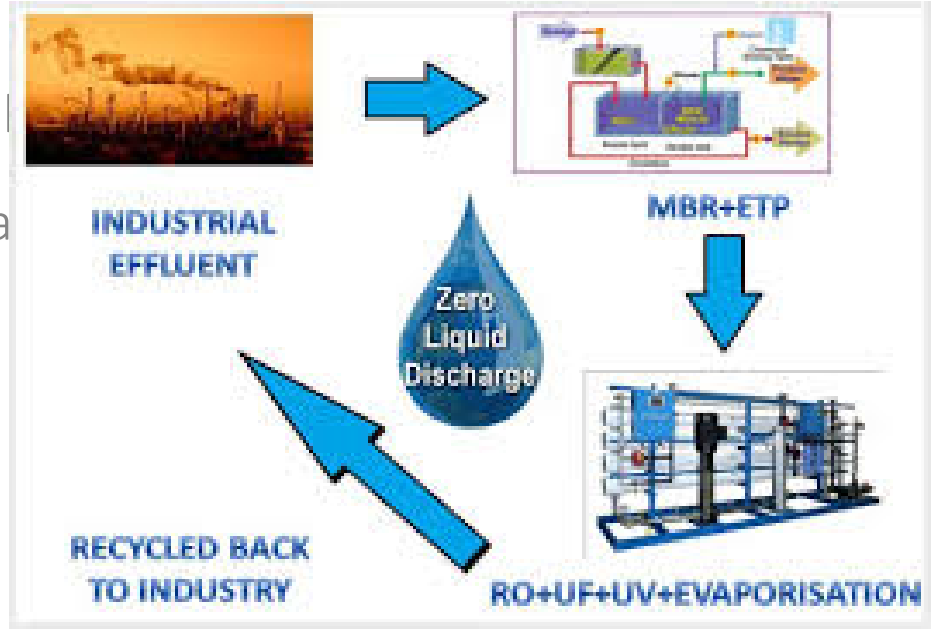
- 'Polishing' step after WWTP
- 'All inclusive'
- No GMP (outside plant)
- $$$

EXAMPLE
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

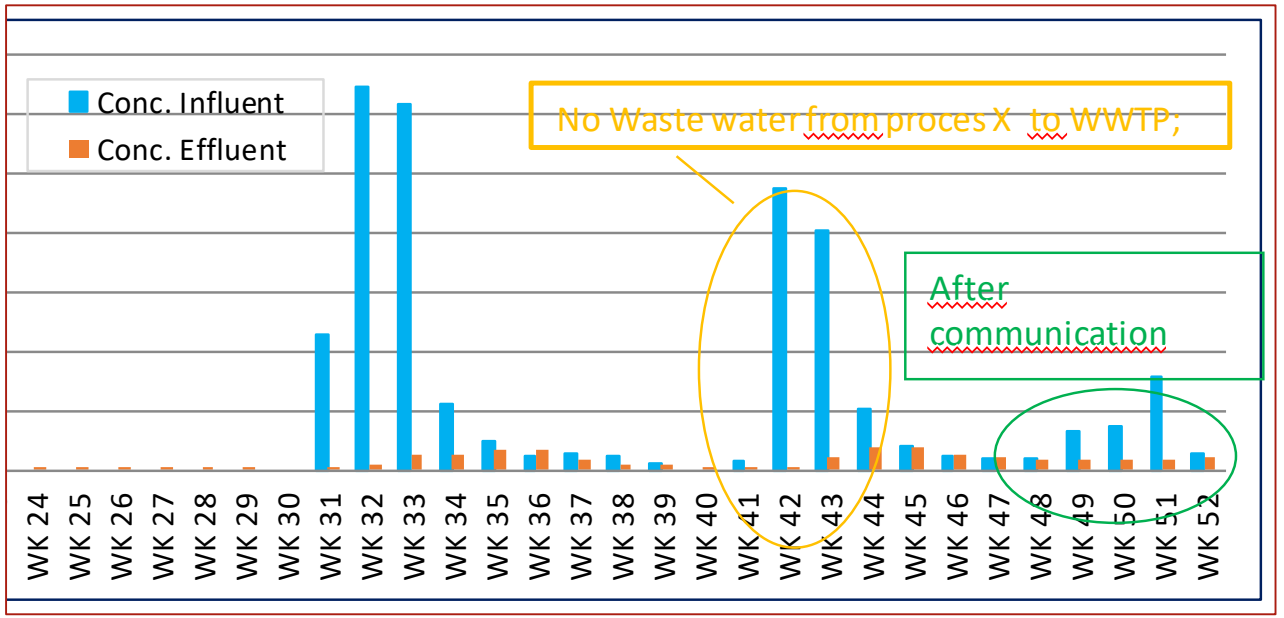
- ZLD Doesn't always equal 'zero risk'. Ground dispersion may resul in:
  - Dermal/inhalation exposure to applicator and/or recreationa users
  - Edible vegetation and/or groundwater users
  - Terrestrial organisms
  - Mist inhalation from opened cooling uses



Zero Liquid Discharge

EXAMPLE
At source mitigation @ API chemcial manufacturing plant

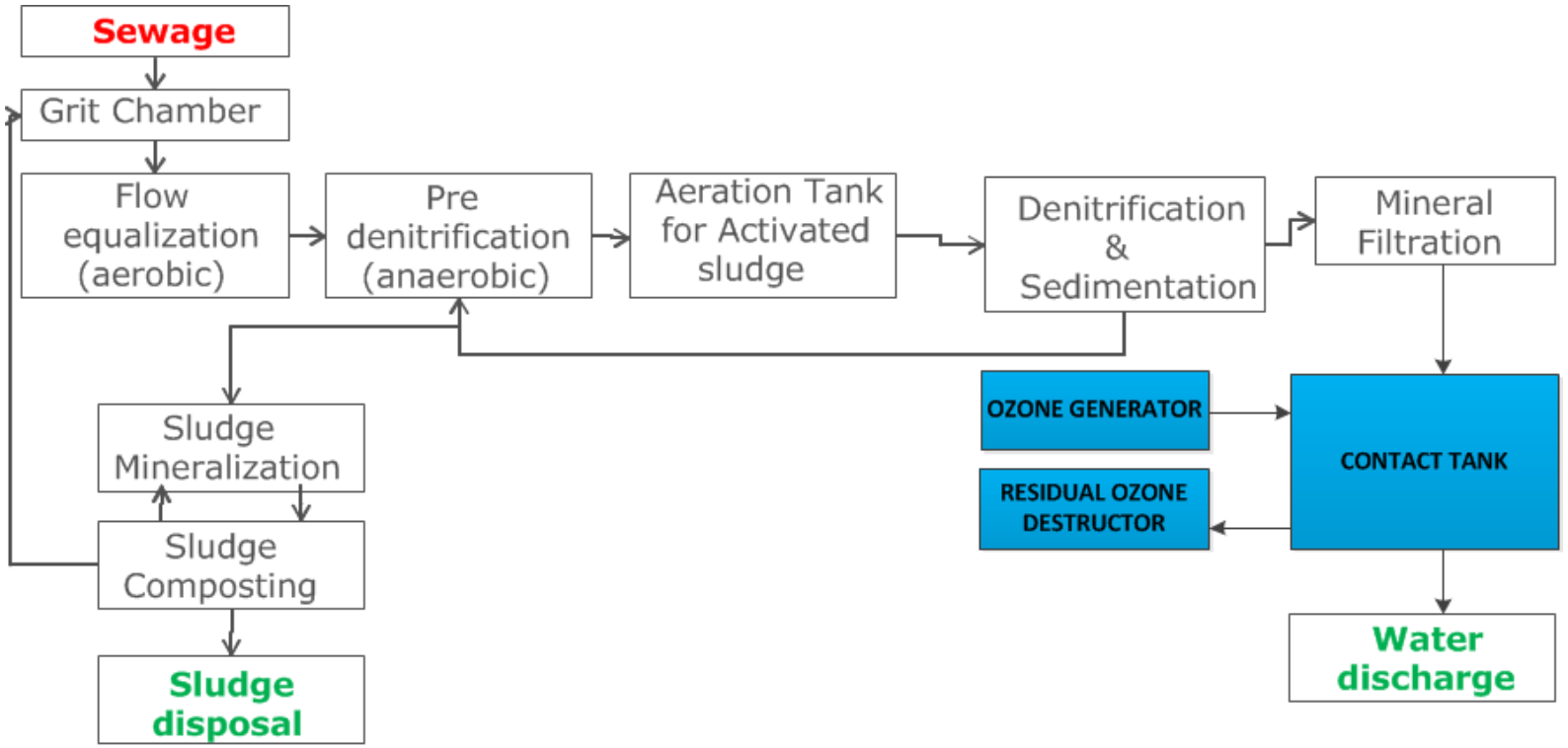
- Discard process wastewater with ‘problematic compound X’ to incineration instead of WWTP
- Investigation with procesmanager → during emptying of centrifuge, some product falls on floor and is flushed to sewer → include good practice in SOP to avoid flushing residual powders in sewer



EXAMPLE
Pre treatment @ API chemcial manufacturing plant : mobile equipment to treat process streams

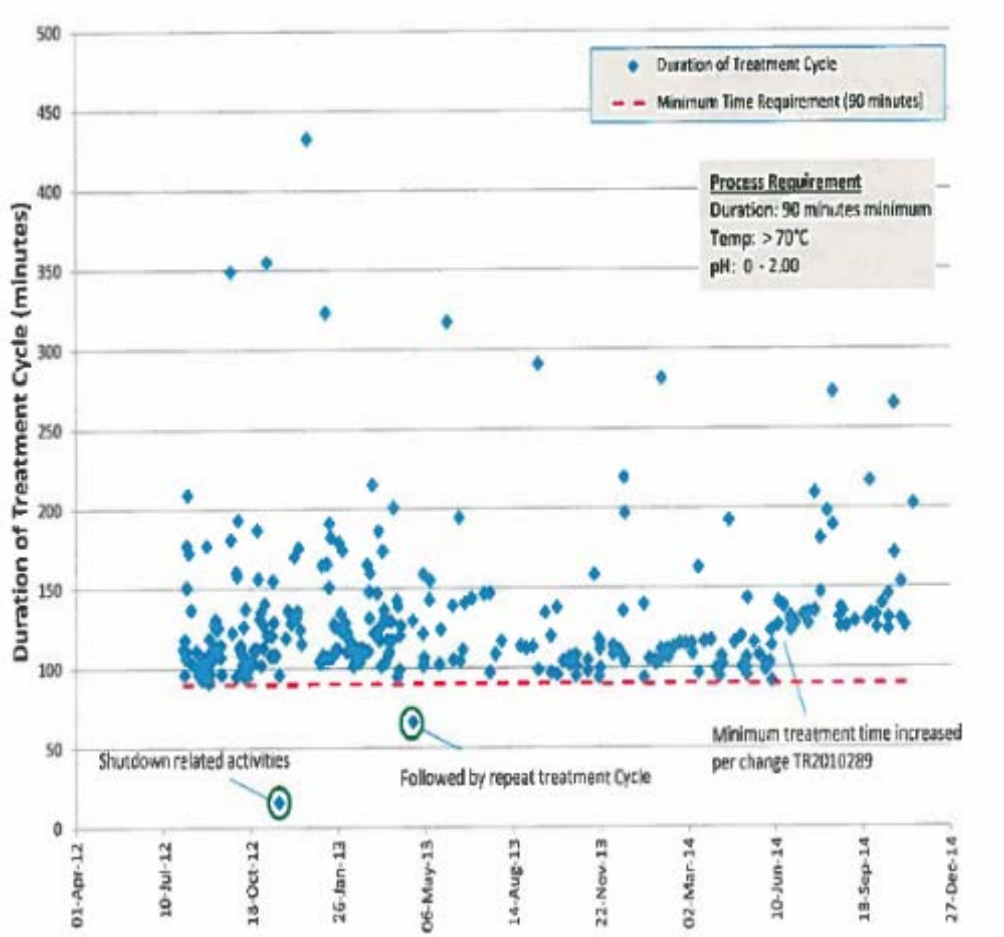
- Remove API from production wastewaters with modular technology (advanced oxidation/adsorption/etc.)
- Pre-treated water can furter be treated in on site water treatment plant
- Equipment can be trucked to other locations (other plants e.g.)

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



EXAMPLE
On-site Treatment Removal Performance of API

- 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

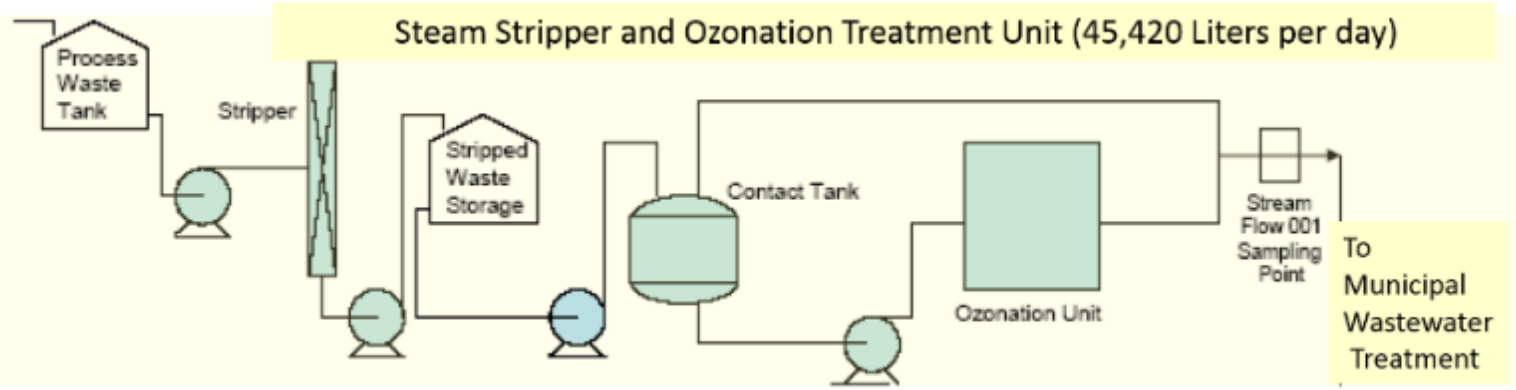


EXAMPLE Audit Questions to Consider:

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)?

EXAMPLE
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

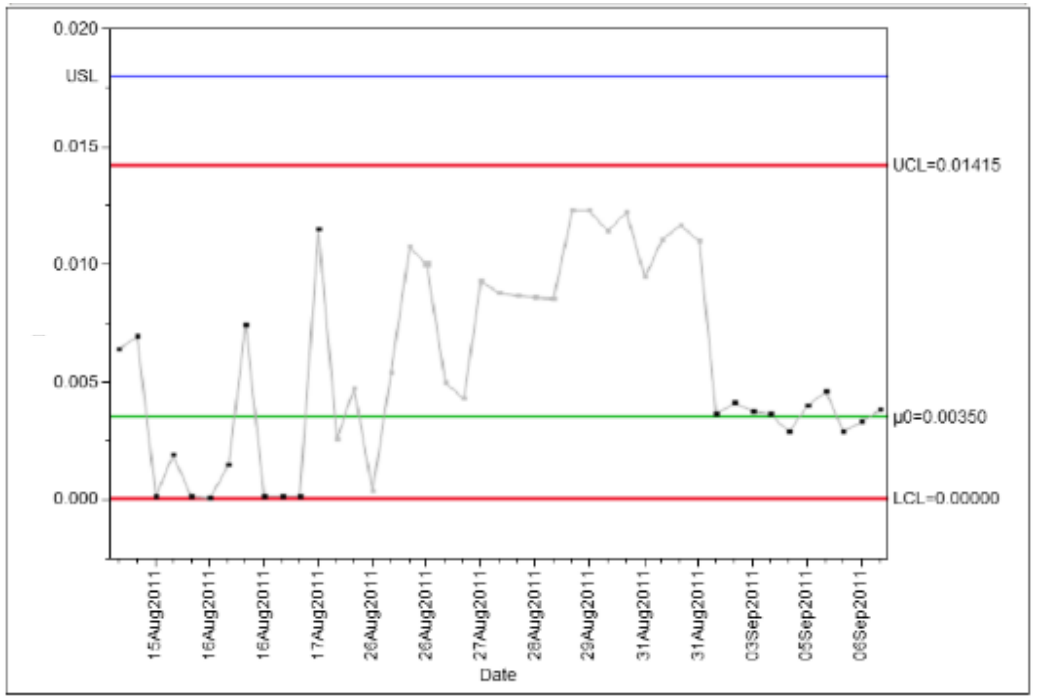
For Product B

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)

EXAMPLE
On-site Treatment and Control of API Discharge

- Large Scale Batch Ozonation
- Greater than 93% API destruction
- Batch processing

Risk Quotient at site final discharge – PNEC $_{acute}$	Risk Quotient at site final discharge – PNEC $_{chronic}$
< 0.211	<0.762



EXAMPLE Audit Questions/Actions to Consider:

1. What were the PNEC values used in these calculations? Were the PNEC values developed by the site or provided by another source? Check the source and background values behind setting the PNEC values.
2. Is appropriate staffing provided to manage and implement programs to control emissions of active ingredients?
3. What are the business area's written qualifications for persons performing and reviewing environmental calculations and running the treatment system.
4. How were the process requirements for ozonation system (ozone concentration and reaction time) determined? How does the site ensure that the wastewater content is not changed to impact treatability?
5. Is the treatment system manually operated?
6. Are other physical barriers (plugged floor drains) in place and do all API containing wastewaters go to this ?

EXAMPLE
Results of Refined PEC Estimates

CASE EXAMPLE Assumptions:

Maximum API loss rate: 0.5 kg/day API
Municipal discharge flow rate: 10,000 m^3/day
River low flow rate: 20,000 m^3/day
Fraction of river allowed for mixing: 0.5
Drinking water Intake flow: 100,000 m^3/day

PEC at Point of Application	PEC – No Removal	PEC – After On-Site Treatment	PEC – After On-site and Municipal Removal
PEC_{acute}	50 ug/L	2.5 ug/L	1.4 ug/L
$PEC_{chronic}$	25 ug/L	1.25 ug/L	0.7 ug/L
$PEC_{drinking\ water}$	0.02 ug/L	0.001 ug/L	0.0006 ug/L

EXAMPLE Audit Questions/Actions to Consider:

1. What were the PNEC values used in these calculations? Were the NEC values developed by the site or provided by another source? Check the source and background values behind setting the PNEC values.
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About the Secretariat
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