Webinar will be recorded

IAI PiE Task Force Responsible Manufacturing Effluent Management

Webinar Technical Guidance Document

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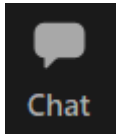
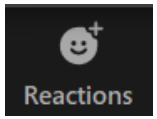
Webinar practical information

- Please **mute your microphone** 
- Please **turn off your camera** 
- Please post your **Q&A questions** in the Chat function at anytime as follows: “Name, Affiliation: Question” 

- Posted questions will be picked up by the **moderator** in the Q&A session
- During Q&A session ask questions by **raising your hand** (Reactions/raise hand) 

- **Slides** and **recording** will be shared after the event

Content

- Introduction
  - PiE
  - Eco-Pharmaco-Stewardship (EPS)
  - Policy statement on Responsible Manufacturing Effluent Management
  - Technical Guidance Document
- Key elements of Technical Guidance Document
  - including Case Studies
- Q&A

INTRODUCTION

How do pharmaceuticals enter the environment?

Pathways to the main compartment "water"

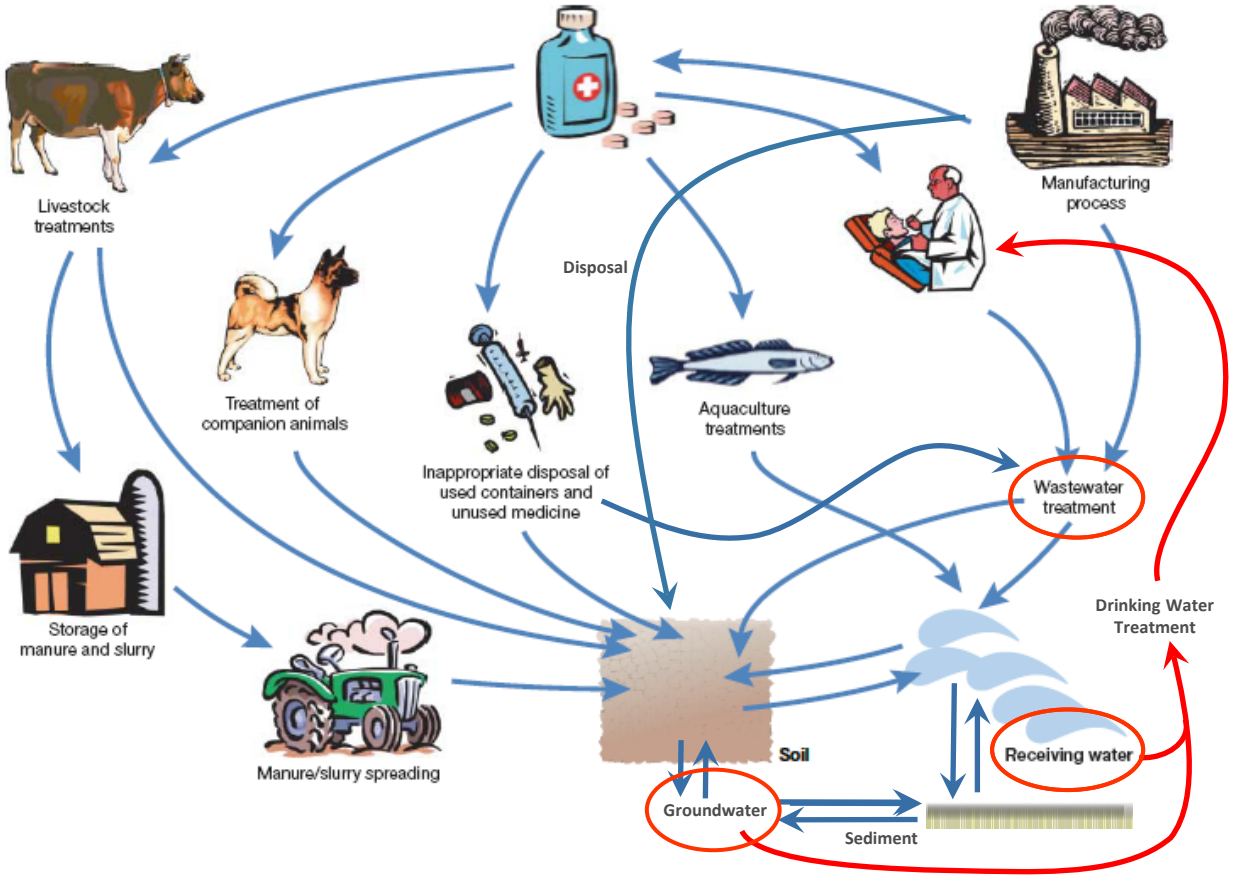
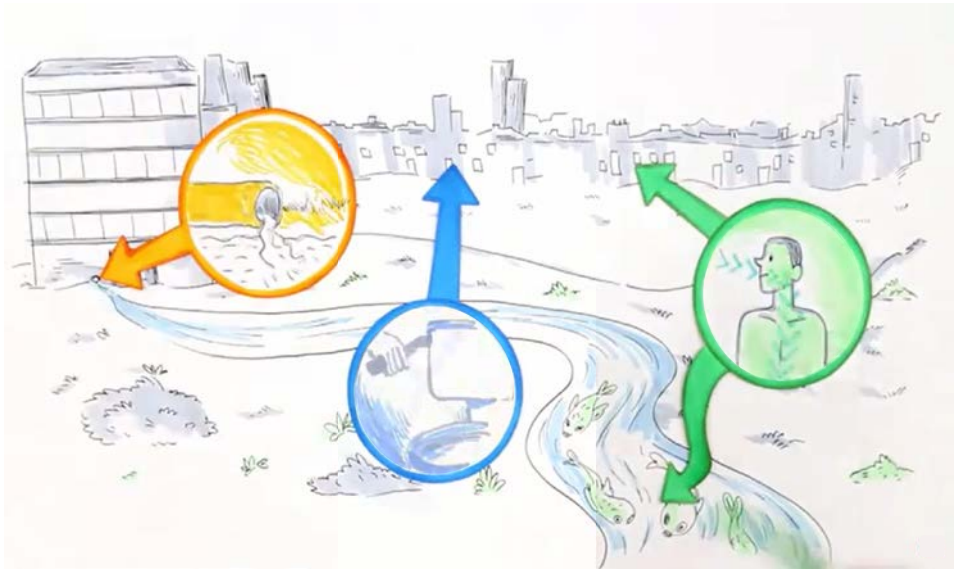


Figure: Boxall ABA (2004): The environmental side effects of medication. EMBO Reports 5(12): 1110–1116, amended

How do pharmaceuticals enter the environment?

Human pharmaceuticals in waters: sources and relative contributions



- Of the 3 main routes for PiE, studies have shown that discharge from manufacturing processes is by far the lowest contributor on a global scale
- However, examples have been noted where high levels of pharmaceuticals from manufacturing were measured from uncontrolled or poorly controlled effluents in localized areas

Graphics by AstraZeneca plc, courtesy Prof Jason Snape
https://www.astrazeneca.com/sustainability/environmental-protection/pharmaceuticals-in-the-environment.html

European Pharmaceutical Industry Collaborations on Pharmaceuticals in the Environment (PiE)

- Inter Association Initiative (AESGP/Efpia/Medicines for Europe) PiE Task Force
  - Eco-Pharmaco-Stewardship (**EPS**)

Filling the knowledge gap through further research and innovation	***Improving current environmental risk assessment***	***Responsible manufacturing effluent management***	***#Medsdisposal***
iPiE PREMIER	Extended Environmental Risk Assessment (eERA)	- Maturity Ladder* - Responsible manufacturing effluent management guidance	MEDS DISPOSAL

- International Industry AMR Alliance Scientific Workstream (www.amrindustryalliance.org) **

* Caldwell DJ *et al.* (2016): A risk-based approach to managing active pharmaceutical ingredients in manufacturing effluent. Environ Toxicol Chem *35:* 813–822. https://setac.onlinelibrary.wiley.com/doi/full/10.1002/etc.3163

** AMR PNEC list: https://www.amrindustryalliance.org/shared-goals/common-antibiotic-manufacturing-framework/

Policy Statement Responsible Manufacturing Effluent Management

- Compliance with local laws, regulations and environmental permits is a **prerequisite** for all API and drug product manufacturing operations.
- Additionally, the member companies of AESGP, EFPIA and Medicines for Europe have developed a set of **principles** for responsible effluent management **for their own, and supplier, manufacturing sites** which focus on the following areas:
  - Compliance with applicable company standards
  - Implementation of defined wastewater management programs that are based on risk management and good engineering principles
  - Definition of site and API specific discharge targets based on safe concentrations in the receiving surface waters
  - Discharge of manufacturing wastewater containing API must have an environmental risk assessment

Technical Guidance Document Responsible Manufacturing Effluent Management

- **Complements** the Policy Statement on Manufacturing Effluent Management
- Is for **internal use** at member companies and their suppliers
- Describes **how** a (future) program can be implemented
- Includes a methodology on effluent risk assessment & mitigation as its **core part**
- Provides a **framework** for “sound wastewater management” around the core part
- Provides **flexibility** for existing member company approaches while ensuring there is agreement on key methodological decisions (comparability of approaches)

Structure of the Technical Guidance

1. Introduction
2. Wastewater management programs
3. Setting, meeting and monitoring targets for wastewater
4. Environmental risk assessment
    - 4.1 Fundamentals
    - 4.2 Exposure scenarios
    - 4.3 Effects assessment: establishing criteria (PNECs)
    - 4.4 Exposure assessment: calculating PECs
    - 4.5 Determining risk (risk characterisation)
5. Risk mitigation and management
6. Glossary
7. References

Appendix
- A1: Calculating mass balances
- A2: Sampling & analysis
- A3: Calculating dilution factors considering mixing zones
- A4: (External) guidance documents for risk characterization

KEY ELEMENTS OF TECHNICAL GUIDANCE

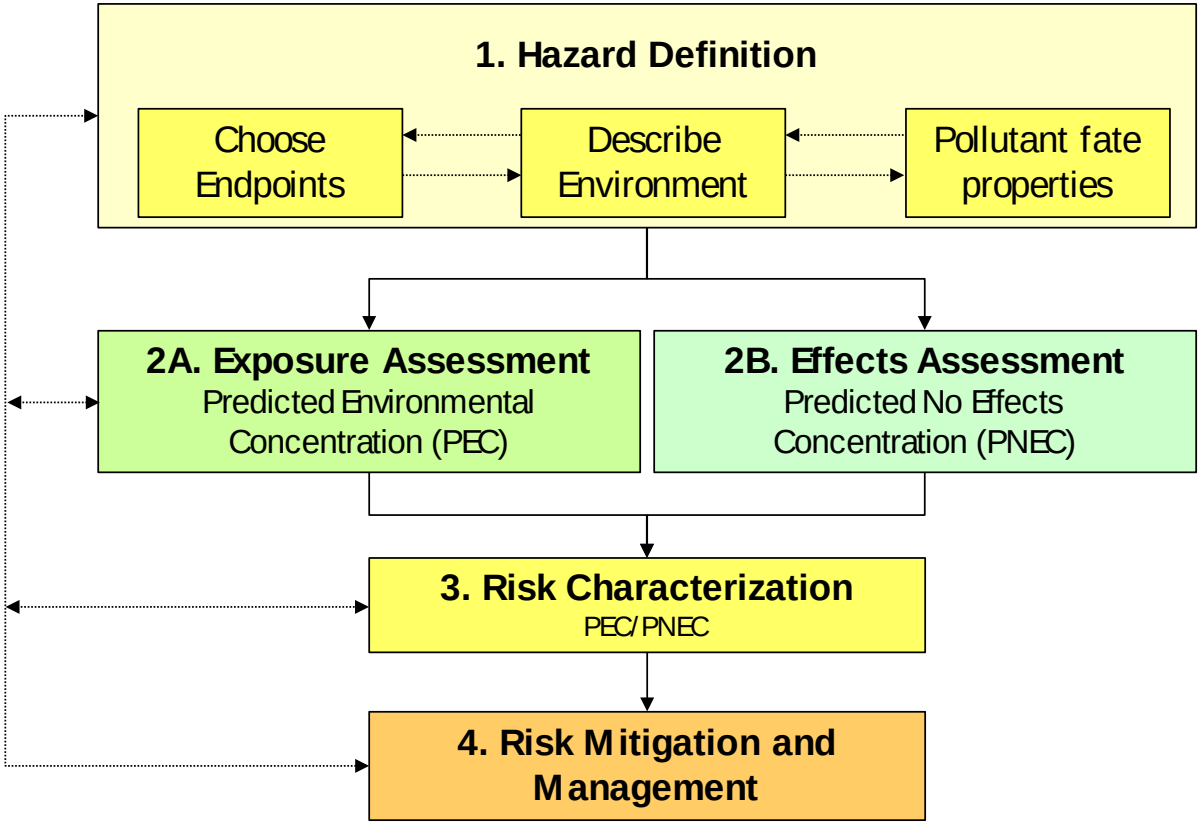
Setting, meeting & monitoring API discharge targets

Definition of site and API specific discharge targets based on safe concentrations in the receiving surface water

Site API Discharge Target = Back calculated from environmentally safe concentration (PNEC) in receiving water and/or other relevant environmental compartments, considering particular site discharge scenario

Environmental Risk Assessment (ERA)

Discharge of manufacturing wastewater containing API must have an environmental risk assessment; if a risk is identified, appropriate additional controls will be implemented to mitigate the risk to an acceptable level.



Receiving water exposure scenarios & criteria (PNECs)

Scenario	Protection goals	Criteria (PNECs)
Effluent discharge (directly or indirectly) to surface water	Aquatic species that live in the surface water	Chronic $PNEC_{surface\ water}$
Effluent discharge involves mixing zone with more concentrated zone compared to chronic exposure (e.g. very large dilution factor in surface water); or short term (pulse) concentrations expected	Aquatic organisms transiently exposed (acute exposure due to travel through mixing zone or intermittent discharge)	Acute $PNEC_{surface\ water}$
Effluent discharge to ocean or sea	Aquatic organisms in saltwater from chronic exposure	Chronic $PNEC_{marine\ water\ bodies}$
Effluent discharge to ocean or sea involves mixing zone with more concentrated zone compared to chronic exposure (e.g., very large dilution factor or pulse concentrations expected	Aquatic organisms in saltwater transiently exposed (acute exposure due to travel through mizing zone or intermittent discharge)	Acute $PNEC_{marine\ water\ bodies}$

The most likely exposure scenario

Other exposure scenarios for receiving waters

Additional potential common exposure scenario's included in the guideline: Drinking Water inlet, Effluent discharge to soil/groundwater, Fishing waters,...

→ Selection of relevant PNECs depends on site-specific discharge & API-specific characteristics

Derivation of chronic PNECs for surface waters

- Dataset to include at least one species from each of the three trophic levels
- Studies to be conducted using standardized methods (e.g., OECD) and employing Good Laboratory Practices (GLP). Studies from literature to be used with care given concerns regarding data quality
- Use most conservative result to derive the PNEC
- Assessment factors (AF) applied to lowest toxicity value to take into account uncertainties associated with the test species and measured endpoint.

$Chronic\ PNEC_{surface\ water}$

Available data	Assessment factor
At least one short-term L(E)C_{50} from each of three trophic levels (fish, invertebrates(preferred *Daphnia*) and algae)	1000
One long-term EC_{10} or NOEC (either fish or *Daphnia*)	100
Two long-term results (e.g. EC_{10} or NOECs) from species representing two trophic levels (fish and/or *Daphnia* and/or algae)	50
Long-term results (e.g. EC_{10} or NOECs) from at least three species (normally fish, *Daphnia* and algae) representing three trophic levels	10

Case study - Risk Assessment
Deriving Chronic PNEC surface water

Initial acute testing, conducted in Phase 2 of the drug development process resulted in a PNEC of 0.012 mg/L.

Chronic testing conducted in Phase 3, resulted in an increase in the PNEC to 0.95 mg/L. For non-regulatory (legacy) compounds, acute testing will be conducted and chronic testing only if sites cannot meet the PNEC and refinement needed. Testing budget put aside for this type of work.

Figure 1




API 1
Acute testing
Lowest LC50/EC50 = 12 mg/L
Assessment Factor = 1000
PNEC = 0.012 mg/L

Figure 2




API 1
Chronic testing
Lowest NOEC = 9.5 mg/L
Assessment Factor = 10
PNEC = 0.95 mg/L

Where to find ecotox data and PNECs
PNECs in case of absence of ecotox data

- Public ecotox data - PNEC sources

EPAR, Fass.se, iPiE-Sum, WikiPharma database, AMR Industry Alliance, WET Center, ECHA, Safety Data Sheets, Vestel *et al.* 2016, Tell *et al.* 2019, Gunnarsson *et al.* 2019, Roos *et al.* 2012, Le Page *et al.* 2017, Bengtsson-Palme & Larsson 2016

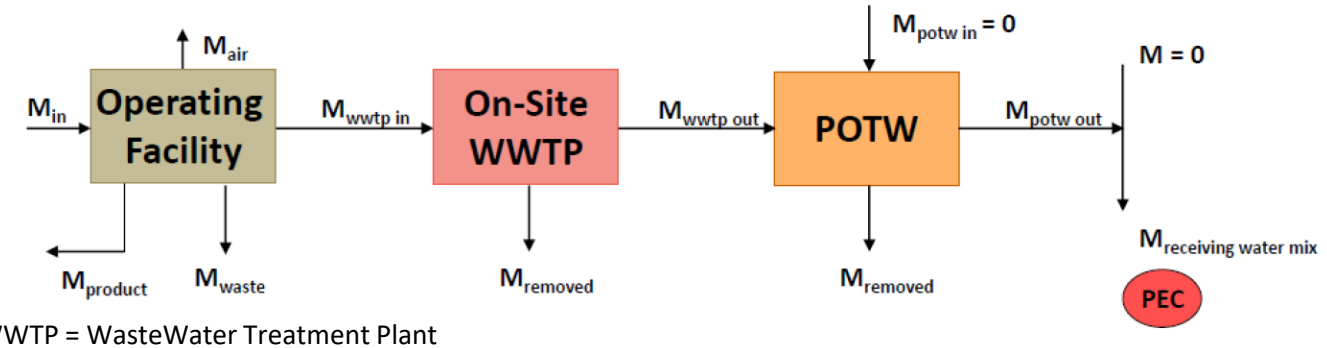
- In case no ecotox data
  - Read accross
  - Default PNEC

  → Several approaches : importance of scientific expertise

Calculating PECs - Determining API losses - Factoring in dilution

$$PEC = \frac{\text{API Loss}}{\text{Reduction and dilution factors}}$$

- Reduction: predicted treatability
- Dilution: high volume drives concentration down



WWTP = WasteWater Treatment Plant
POTW = Publicly Owned Treatment Works. Can also be other type of off site WWTP (privately owned/shared)

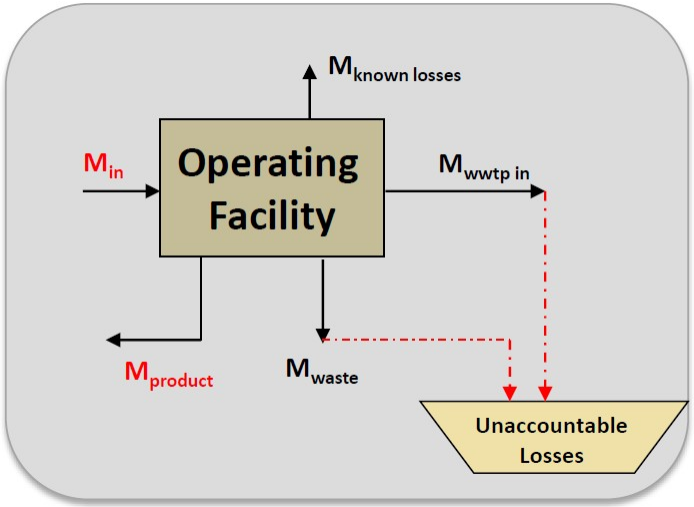
$$Mass\ (M) = Flow\ (Q) \times Concentration\ (C)$$

$$DF = (Q_{effluent} + Q_{upstream}) \div Q_{effluent}$$

PEC = Environmental background + effluent (process contribution)

Calculating mass balances

- Information about waste streams can be sourced from process descriptions, batch records, technical service reports, etc.
- Concentration estimates can be derived from API masses and volumes involved e.g., mass in lot/batch, maximum daily losses based on number of batches/day and cleanings/day, etc.



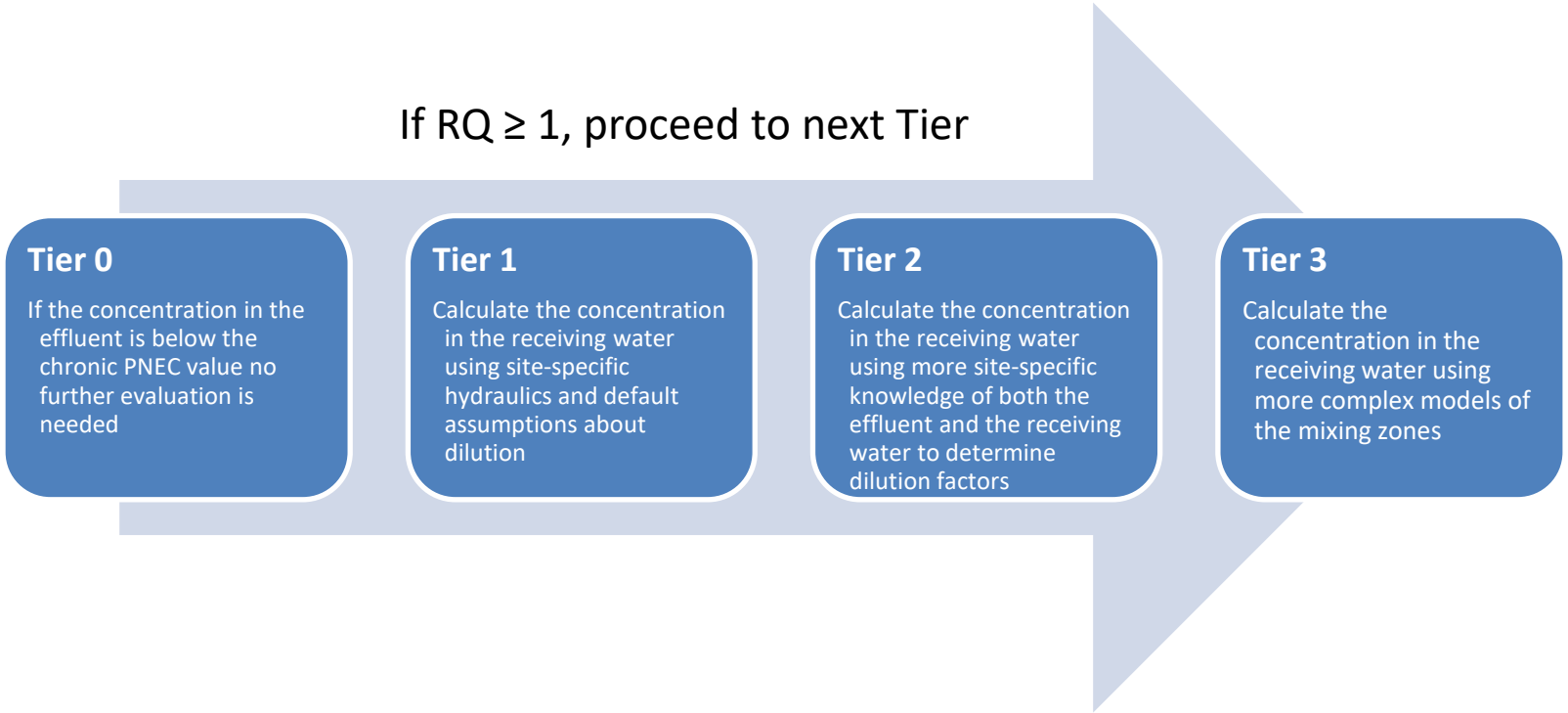
Factoring in dilution form the receiving water

- Recommended to use low flow conditions e.g.
  - EU: 10th percentile flow rate from the previous 7 years or 1/3rd average flow
  - US: 7Q10 flow, i.e. smallest value of average discharge over 7 consecutive days over a 10 year period

- Evaluate applicability of ‘mixing zone’: Some local regulators may place a limit on the proportion of the channel width or the stream flow that can be used for dilution

Determining risk - Calculating the Risk Quotient (RQ) Tiered approach

RQ = PEC/PNEC



Case study - Risk Assessment
Tiered approach using refined exposure/dilution data

A conservative company specific default dilution factor for marine discharges of 10 was implemented. This resulted in a PEC/PNEC >1 **(Figure 1**)

To refine the risk assessment the dilution in the marine environment was investigated. The local WWTP was contacted and a dilution factor of 136 was found to be permitted. Resulting in a PEC/PNEC <1 **(Figure 2)**

Figure 1

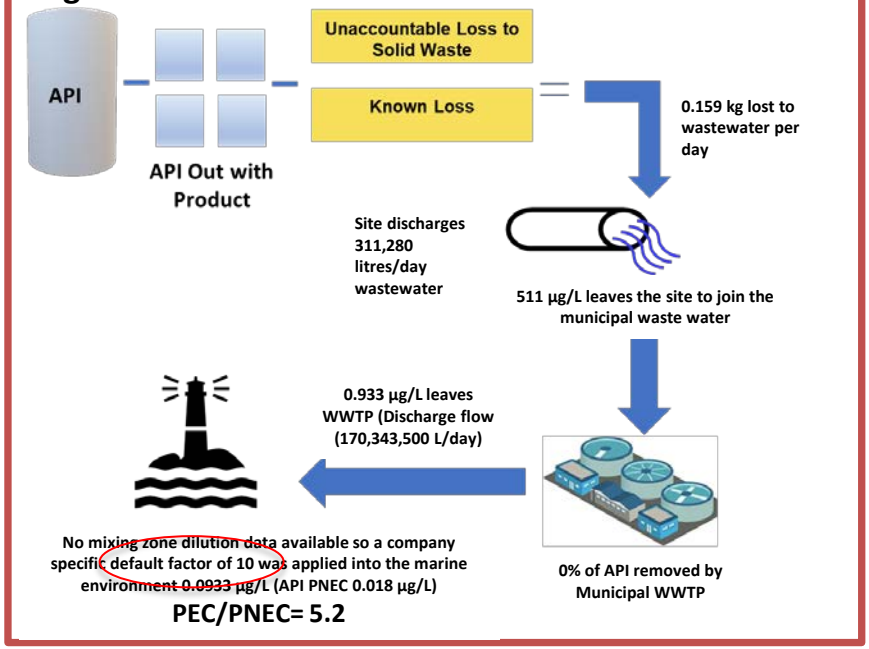
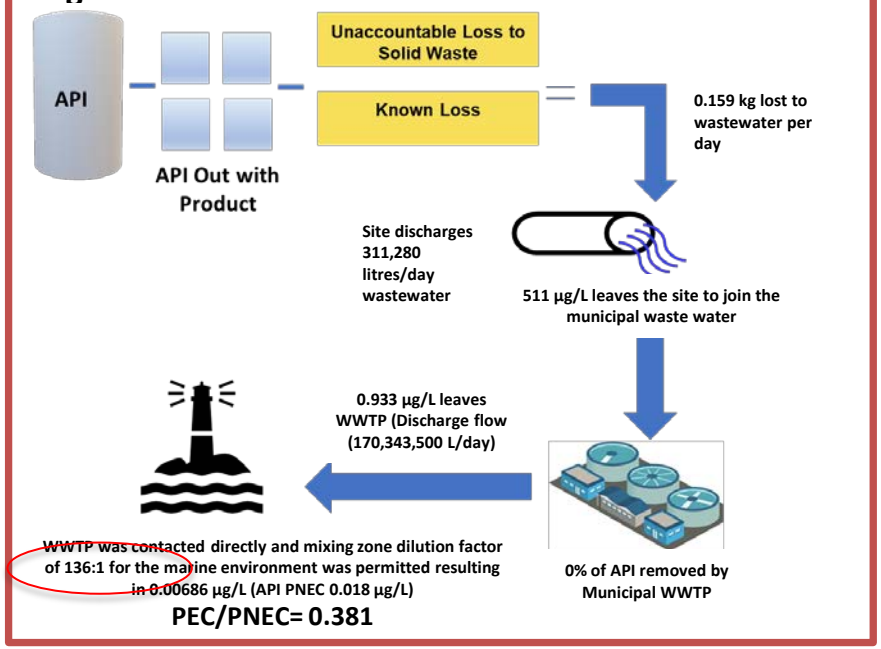


Figure 2



Measuring APIs in site effluent

Chemical analyses to determine actual concentrations may be conducted to remove uncertainty

- Consider the point of sampling

Point of generation	versus	WWTP effluent
Less analytical sensitivity required		more representative for discharge concentration

- Sampling during typical manufacturing campaign, including cleaning

Case study - Risk Assessment
Tiered approach implementing analytical sampling

Local authority requested evidence of level of protection of mass balance calculations. Analytical monitoring campaign designed for site effluent and incorporated onward dilution to calculate receiving water body risk

Measured risk quotients were calculated using highest (acute) and average (chronic) measured values. These were compared to mass balance predictions to show a good correlation and that mass balance was suitably protective

Figure 1

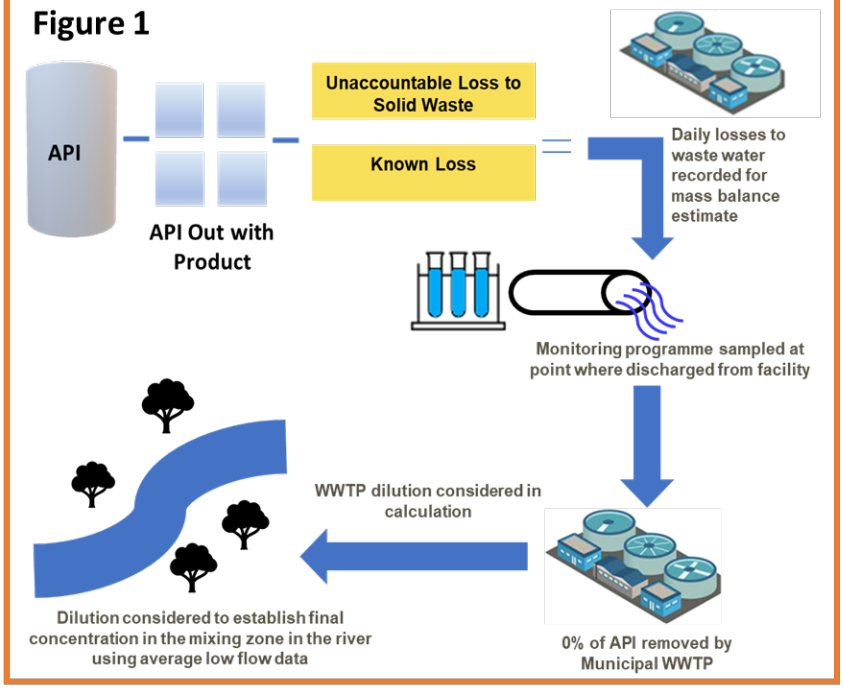
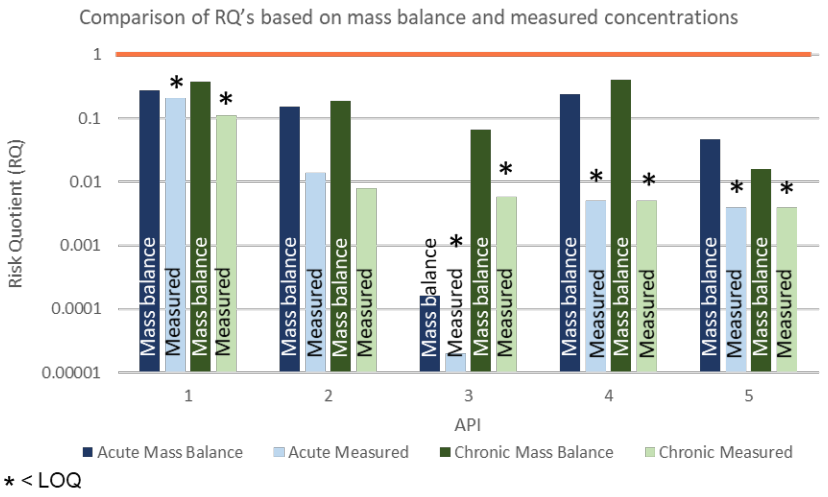


Figure 2

RQs were calculated using a mass balance approach and then confirmed by analytically monitoring APIs in the waste stream. Analytical method limits of quantitation (LOQ) were chosen to ensure measured RQ's <1.



Risk mitigation and management - What if RQ is ≥1?

Risk Quotient		
≥1	Indicates that the expected concentration exceeds the no-effect concentration indicating the potential for impact to the environment	

Release reduction hierarchy

1. Reduce losses to wastewater (e.g. yield improvement, dry cleaning practices)
2. Collect concentrated wastewater at point of generation and implement alternative treatment (e.g. off site incineration, on site pre-treatment)
3. Make WWTP modifications; consider options as pre-treatment and end of pipe treatment (e.g. advanced oxidation, membrane separation)

→ **Re-assess risk**

Case study - Risk mitigation and management Process changes (reduction of losses)

New potent API brought into a dry product tableting plant with very low receiving environment dilution. Mass balance calculations showed that operations could discharge no more than 0.3% of a batch to meet PEC/PNEC of 1.00 **(Figure 1)**

Plant evaluated containment and management practices in the process at source and wrote SOP to require manual clean out (vacuum/wiping equipment) of equipment if mass balance losses would be greater than 0.3% **(Figure 2)**

Figure 1

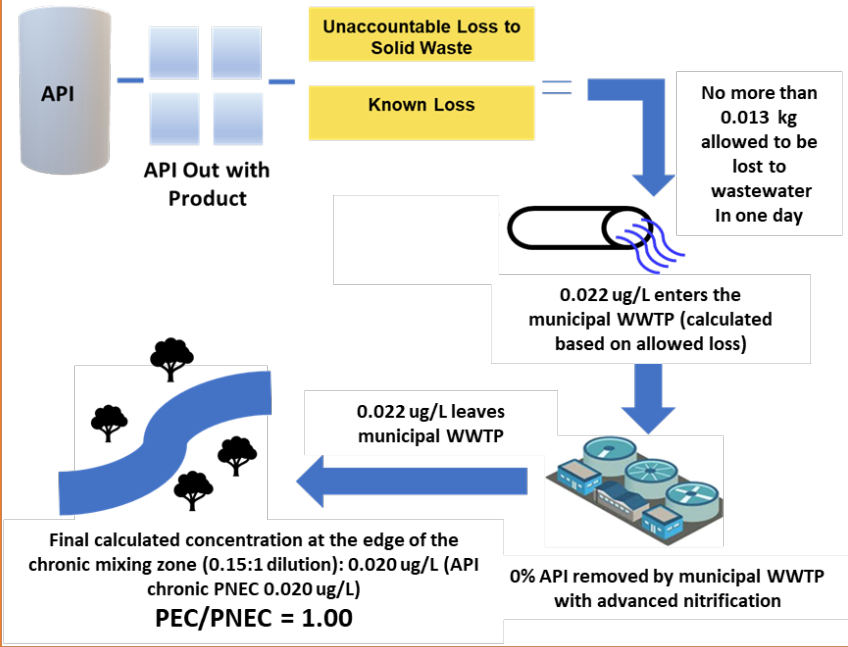
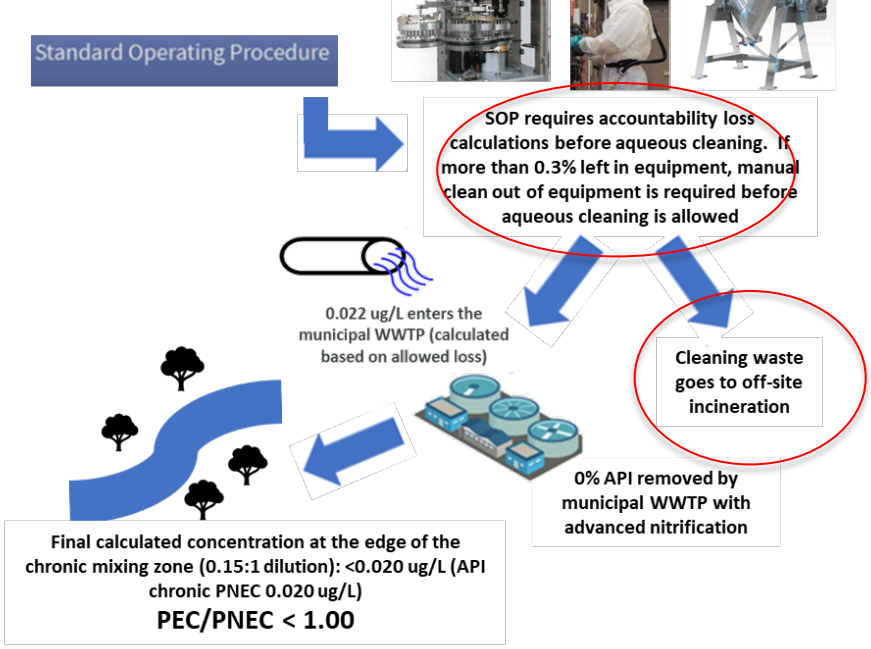


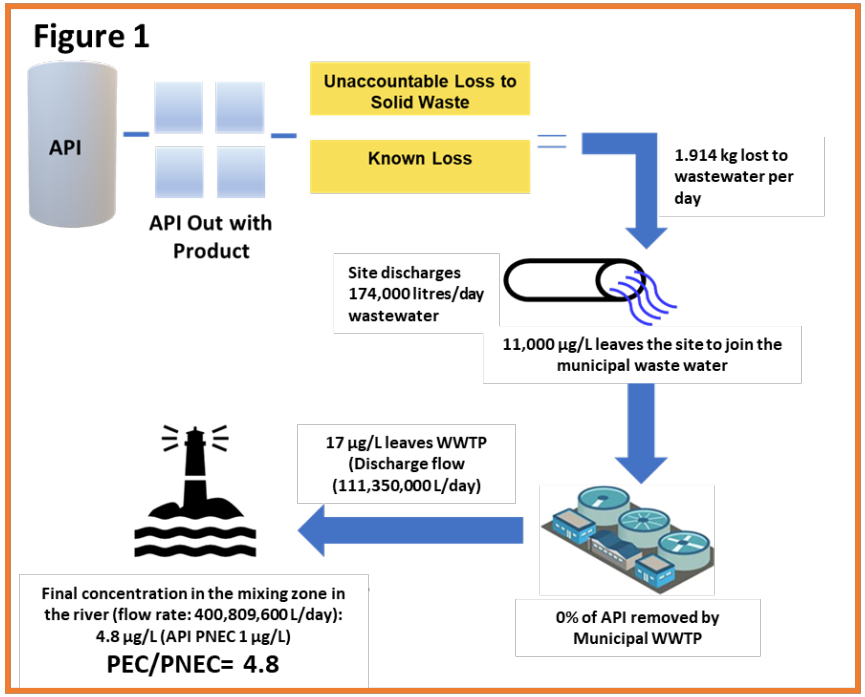
Figure 2

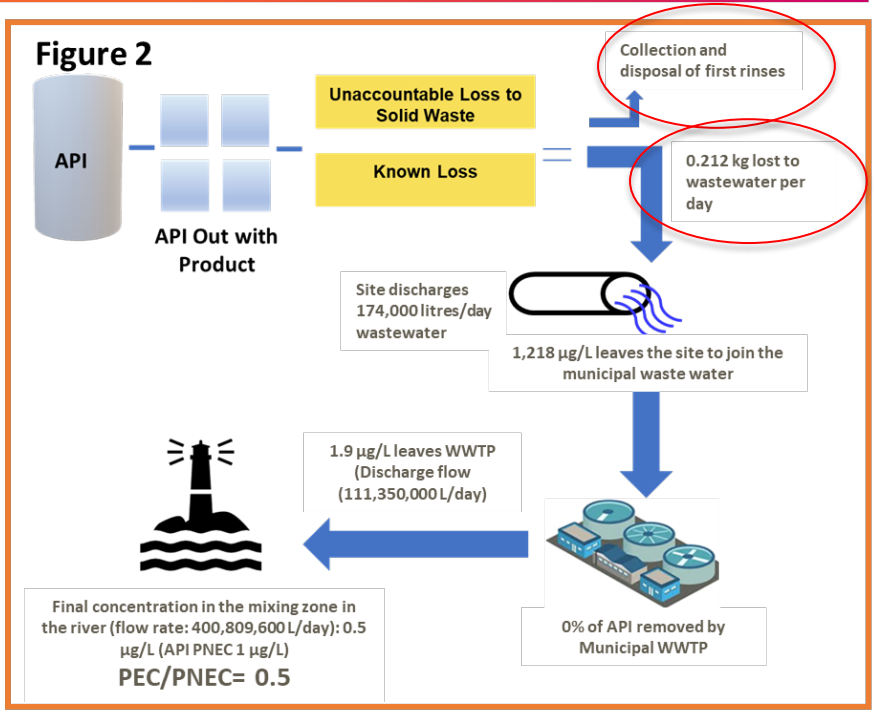


Case study - Risk mitigation and management Collection of first rinse

Discharge of API in receiving water found to be above PNEC **(Figure 1: PEC/PNEC=4.8)**

Site introduced collection and disposal of water used for cleaning and first rinses reducing the quantity of API to waste almost 10-fold (**Figure 2: PEC/PNEC=0.5**)





Case study - Risk mitigation and management Wastewater treatment process

Discharge of antibiotic in wastewater found to be above AMR Alliance limit **(Figure 1: PEC/PNEC=6.2)**

Site introduced total containment at source through installing a thin-film evaporator dryer to eliminate residues from process wastewater (**Figure 2: PEC/PNEC=0.16**).

Figure 1

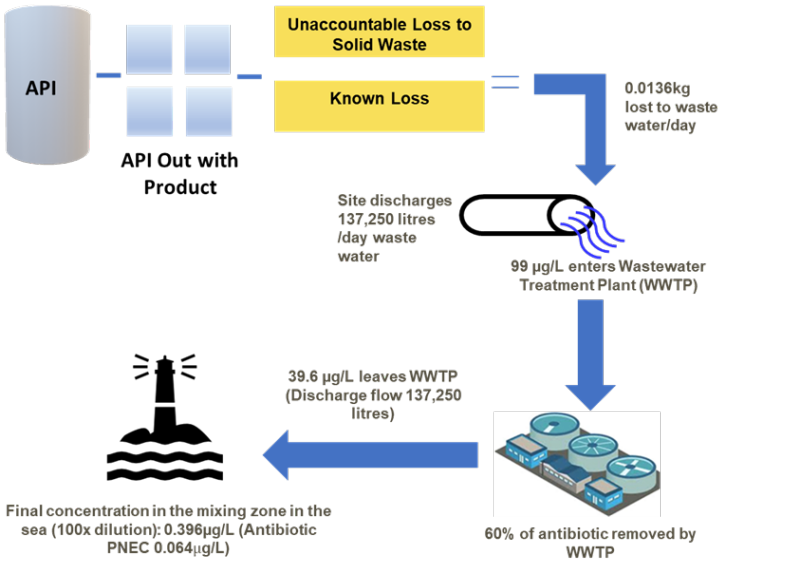
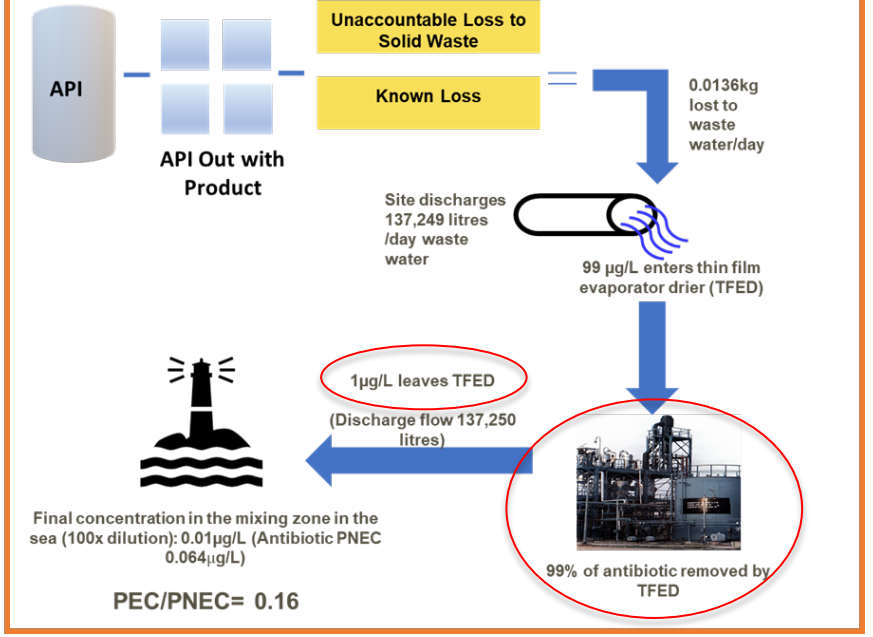


Figure 2



Summary – Key Take Aways

- Although discharge from manufacturing processes has been shown to be the least impactful on a global scale, the Pharmaceutical Industry is **collaborating to do its part** to minimize the risks from pharmaceuticals in the environment from manufacturing facilities
- Technical Guidance Document for Responsible Manufacturing Effluent Management will help member companies to **implement and mature** their PiE program
- Provides a framework for a **step-by-step** approach
- It provides **flexibility** while ensuring alignment on key methodological decisions

Q&A