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Building responsible supply chains

Supplier Water Quality & Pharmaceuticals in Environment (PiE)

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PSCI PiE and AMR Team

Agenda

Global challenge - Water quality & Pharmaceuticals in Environment (PiE)

How to assess PiE risks from manufacturing sites?

Actions required to ensure water quality

Resources available to support

Global challenge - Water quality & Pharmaceuticals in Environment (PiE)

Water Quality is a global challenge

Water pollution is an invisible crisis

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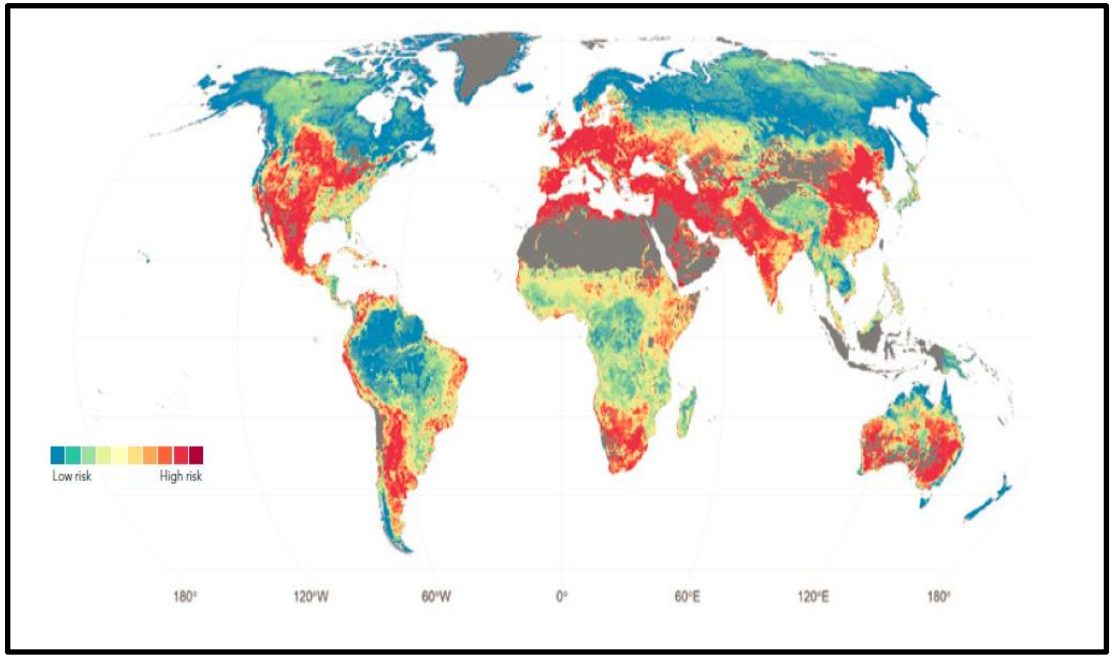
Water quality risk summarizing global predictions for biological oxygen demand (BOD), nitrogen and electrical conductivity



Source: worldbank.org/qualityunknown

Number of APIs detected in surface water, groundwater or drinking water

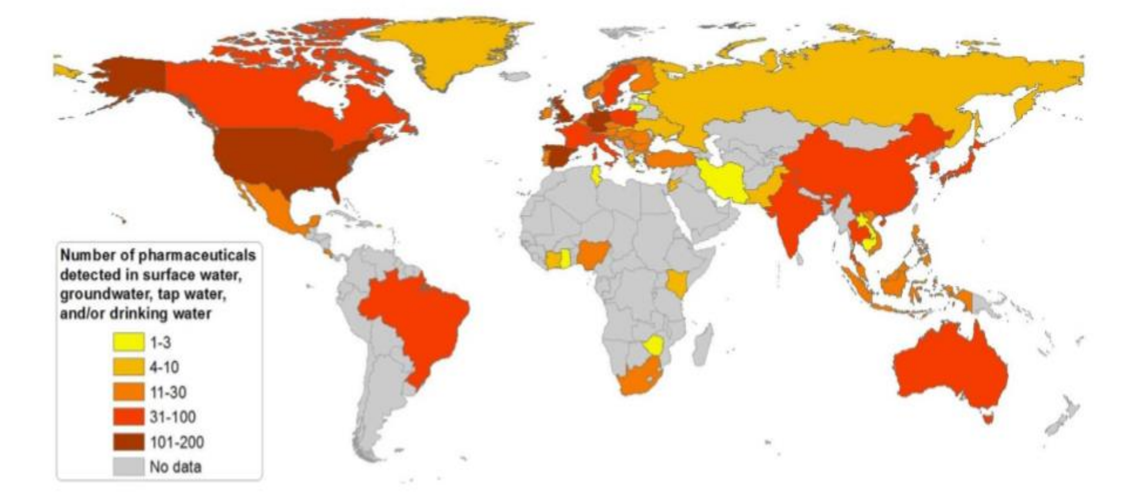


Figure 3. Country survey on the number of pharmaceutical substances detected in surface waters, groundwater, or tap/drinking water.

Source: Environ Toxcicol Chem 35, 2016 -https://pubmed.ncbi.nlm.nih.gov/26666847/

The dilemma of drug products

Active and stable also in the environment

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- safe and
- efficient to improve and extend peoples lives

- biological active in small amounts
- stable in order to reach the target within the patients body

- Patients excrete APIs generally unchanged. APIs get emitted to municipal waste water treatment plants (WWTP)
- When not properly managed, manufacturing effluents contain APIs and will be discharged to WWTP
- Due to their stability, Some API are not “destroyed” via microbial activities within the WWTP and enter the environment unchanged (biologically active and stable)

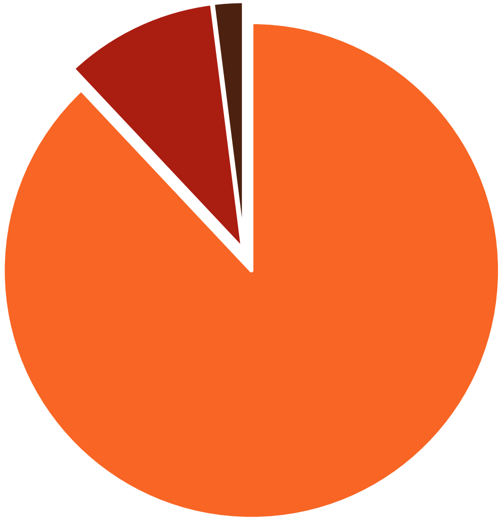
How do pharmaceuticals enter the environment?

Main pathways

Patient use and excretion

Improper disposal

Discharges from manufacturing facilities

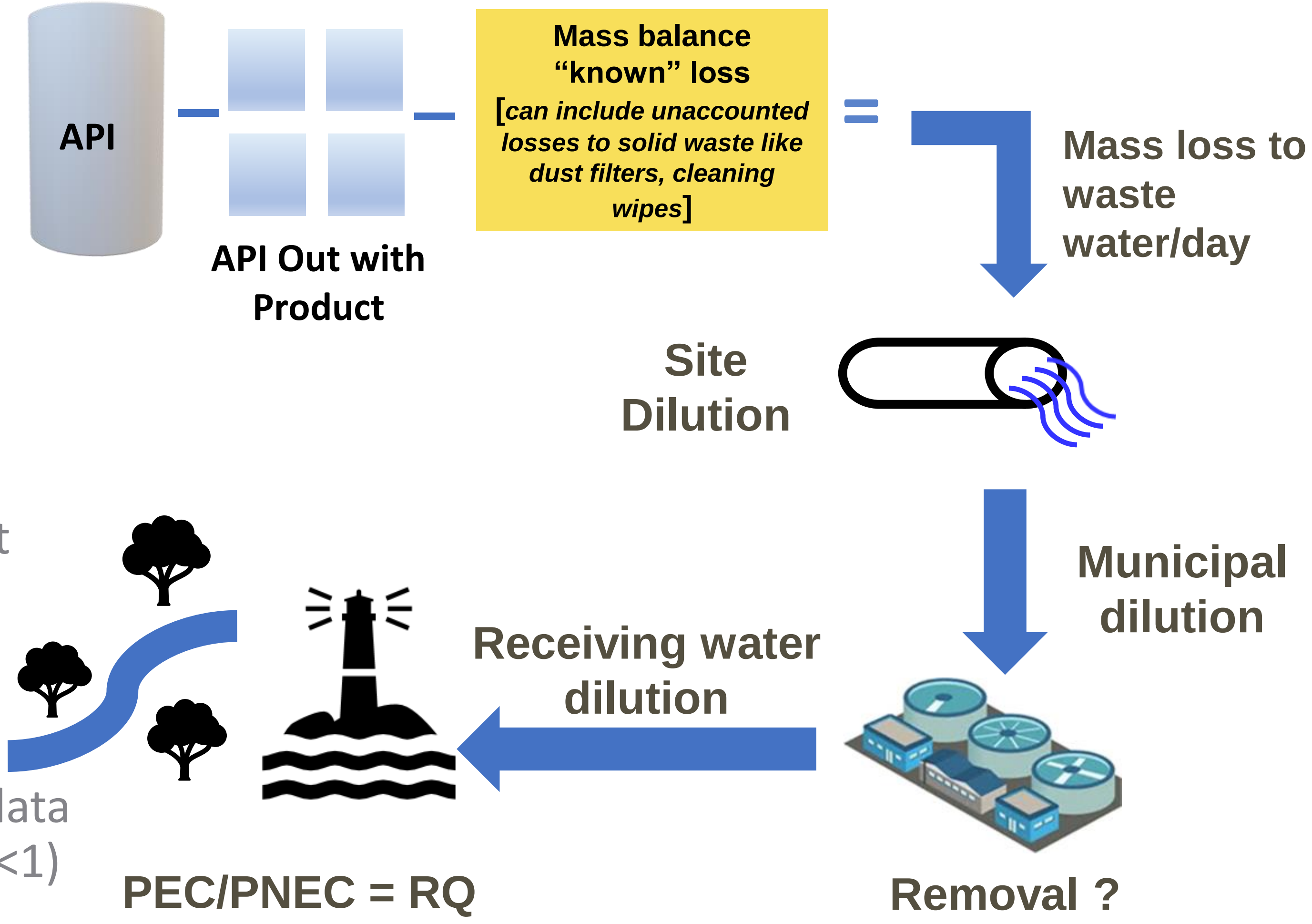


Sources of Pharmaceutical Residues in the Environment and their Control, DANIEL J. CALDWEL https://pubs.rsc.org/en/content/chapterpdf/2015/9781782622345-00092?isbn=978-1-78262-189-8&sercode=bk
IAI PiE Task Force Pillar 2: Manufacturing Effluent Management (efpia.eu)

How to assess PiE risks from manufacturing sites?

How to conduct Effluent risk assessment?

- Utilise a **Mass Balance** approach
- Mass losses assumed into waste water
- Dilution from site waste water and municipal treatment plants
- Removal/degradation at treatment plant
- Dilution in receiving environment
- Compared to PNEC from ecotoxicology data to derive risk quotients (RQ = PEC/PNEC<1) Ensure RQ <1



Mass Balance Process Overview (1/4)

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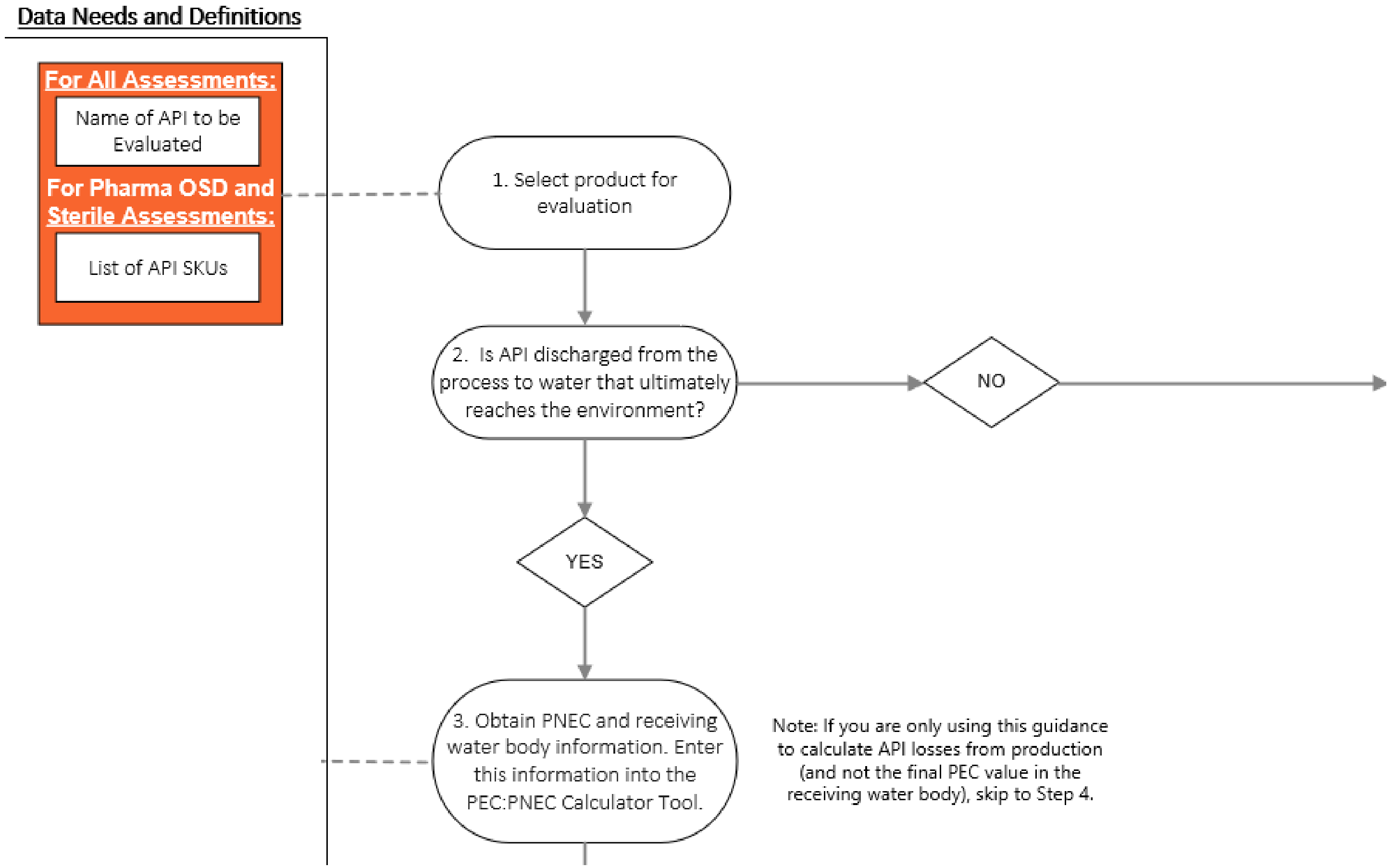
The detailed guidance contains 8 steps. Steps increase in complexity as you go.



Step 1: Select the product and specific SKU for evaluation.

Step 2: Determine if API Losses can be discharged to the environment.

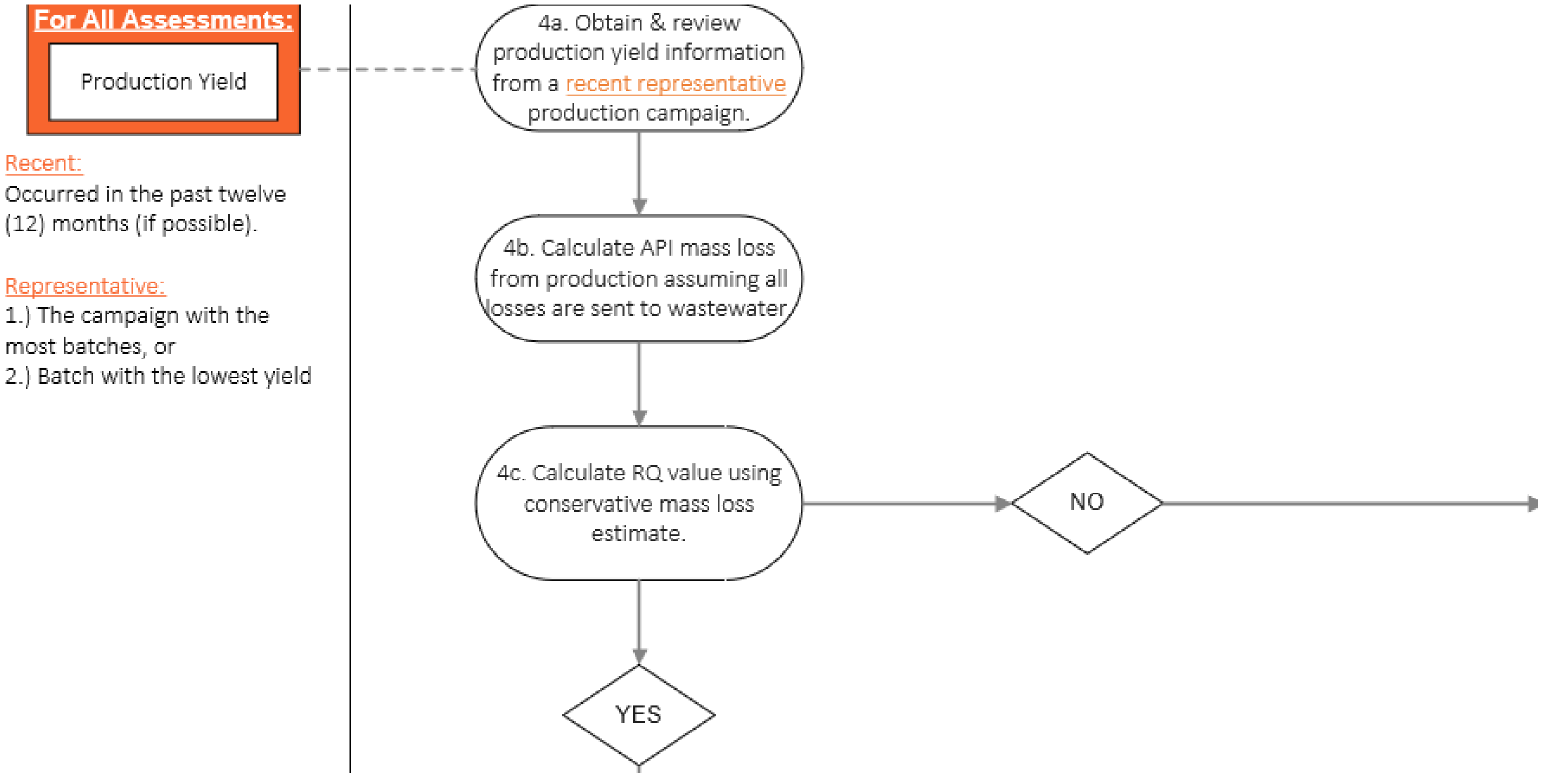
- If possible, continue with assessment.
- If not possible, skip to documentation.

Step 3: Obtain PNEC and River Flow Information

- Select values based on company and/or PSCI guidance.
- **Not necessary to perform mass balance.**

Mass Balance Process Overview (2/4)

The detailed guidance contains 8 steps. Steps increase in complexity as you go.



Step 4a: Obtain batch record information for selected product.

Step 4b: Use batch record information to calculate **eMax.**

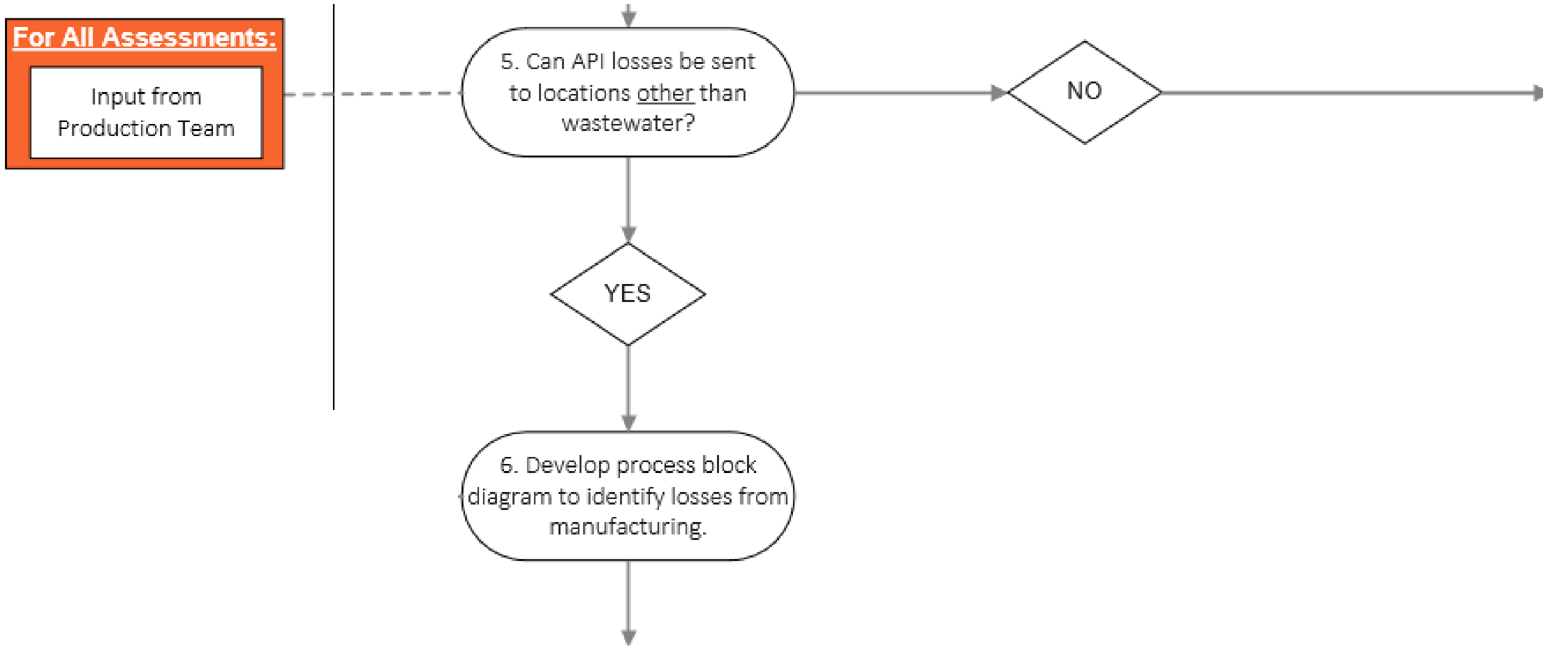
- Assume all losses go to wastewater.
- Conservative, easy to calculate.

Step 4c: Calculate PEC/PNEC (RQ) value using **eMax**.

- If RQ < 1, skip to documentation.
- If RQ > 1, proceed to Step 5 to refine mass loss estimate.

Mass Balance Process Overview (3/4)

The detailed guidance contains 8 steps. Steps increase in complexity as you go.



Step 5: Determine other locations where losses occur.

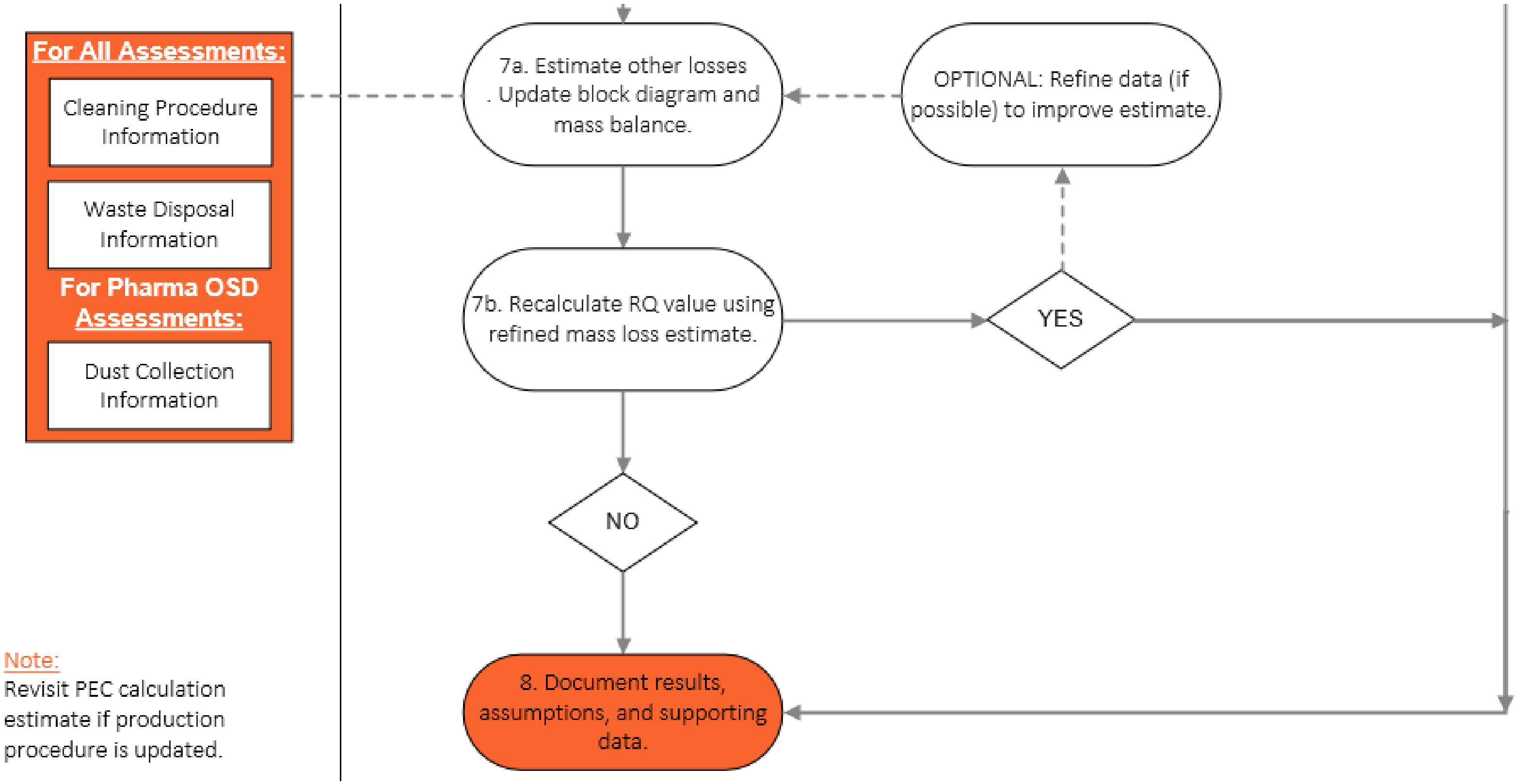
- Dust losses
- Solvent disposal
- Cleaning removal
- QA/QC samples

If there are no other loss locations, then document results from Step 4.

Step 6: Develop a block diagram to track losses associated with production.

Mass Balance Process Overview (4/4)

The detailed guidance contains 8 steps. Steps increase in complexity as you go.



Step 7a: Populate block diagram with process loss information.

- Dust losses
- Solvent disposal
- Cleaning removal

Step 7b: Calculate new **eMax**, RQ values

- If RQ > 1 and further refinement is possible, return to step 7a.

Step 8: Document results and assumptions using standardized template.

PSCI tool for assessing API discharges

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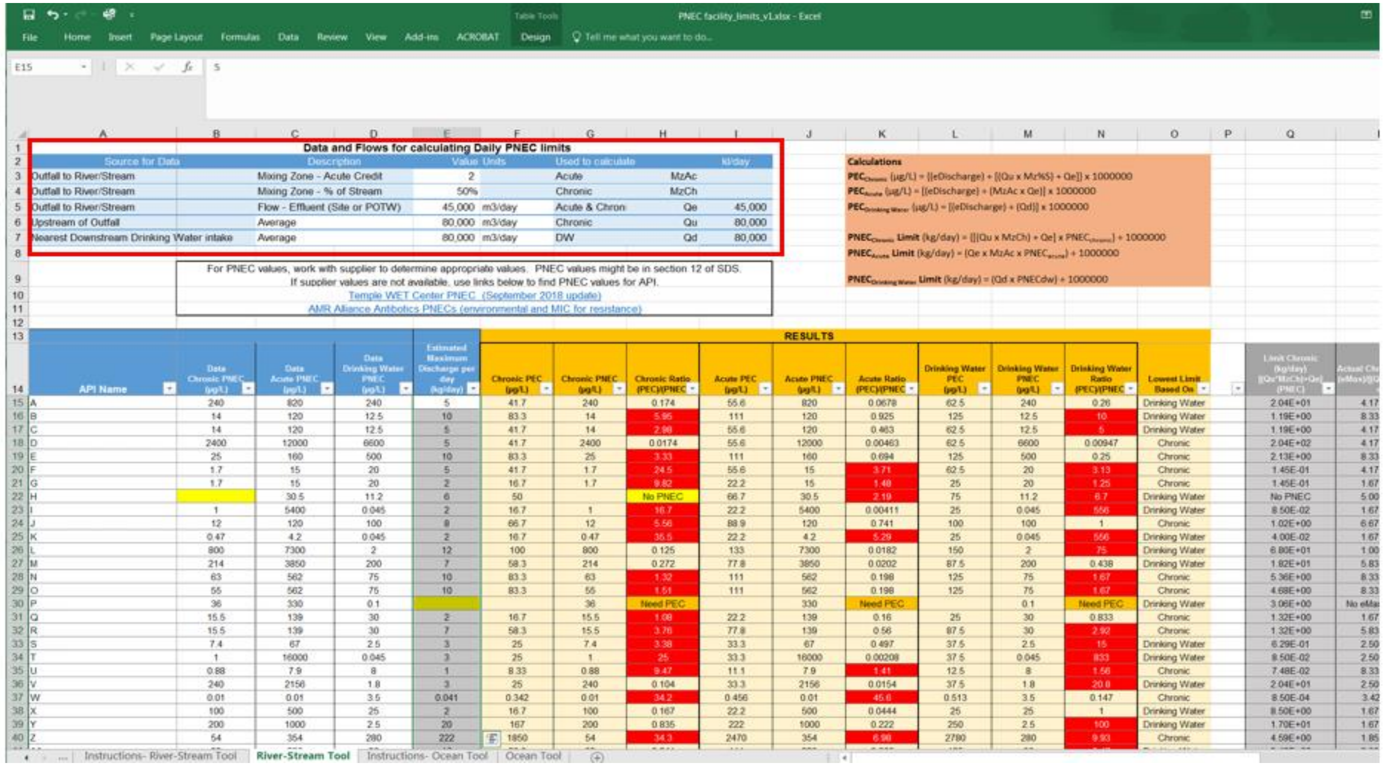
PSCI has published a [PEC:PNEC calculator tool] for manufacturers to use to calculate how to meet safe levels of discharge for active pharmaceutical ingredients (APIs) from their sites.



PEC/PNEC calculator tool

Microsoft Excel Worksheet

Actions required to ensure water quality

PSCI Water Quality (PiE/AMR)

Supplier Maturity Model

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Starting out

- Compliance with law
- Necessary policies in place
- Minimum standards are being met

Developing

Plus

- Audits / baselines / risk assessments complete
- Key risks and highest impacts identified
- Measurement and recording systems in place
- Management responsibility has been allocated
- Targets and objectives set

Implementing

Plus

- Processes in place with clear responsibilities for key staff
- Employees are aware and trained as appropriate
- Targets generally being achieved
- Improvement projects
- External verification
- External partnerships being developed
- Public reporting or other transparency
- Risks are adequately managed

Leading

Plus

- Embedded in culture
- External recognition / awards
- Taking an advocacy stance
- Approach includes whole value chain
- External partnerships across industry
- Supporting partners / customers to improve.
- Sustainability drives innovation
- Sustainability leads to differentiation and commercial advantage

The PSCI maturity models are a roadmap helping suppliers evaluate how responsible their current practices are and what progress against the PSCI Principles looks like.

PiE/AMR Supplier Maturity Model (1/3)

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Starting out

All API Manufacturing and Formulation sites

- **Local laws and regulations**
  - Ensure all operations comply with permits i.e. wastewater discharge limits and landfills /disposal areas are authorized by regulatory authorities
- **Company standards**
  - Codes of conduct include environmental standards
- **Awareness of PSCI Principles**
- **No untreated/unevaluated discharge of manufacturing waste and wastewater**

Antibiotic API & Antibiotic Formulation Manufacturing Sites

- Awareness of the issue of antimicrobial resistance (AMR) and the aims and objectives of the AMR Industry Alliance

Developing

PLUS

- **Familiar with PSCI resource/training materials.**
  - Developing environmental risk assessment (ERA) program
  - Conducting mass balance calculations for API discharges
- **Identify/take action where unevaluated liquid/solid wastes may be released**
- **Assessing suitability of WWT for API discharges**

PLUS

- **AMR Alliance Common Manufacturing Framework:** Evaluate management of antibiotic wastes and other on-site processes that could effect environmental discharges of antibiotic according to the framework

PiE/AMR Supplier Maturity Model (2/3)

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Implementing

PLUS

- **Perform regular review of permit conditions** - strong compliance track record
- **Regular training program**
  - ERA capability building & Data evaluation (mass balance); WWT operation & maintenance
- **Mass Balance**

  -Quantify API loss via mass balance calculations; confirm with analysis of wastewater where needed.
  -Conduct internal audit, take corrective action if API discharges exceed Predicted No Effect Concentration targets
- **Assess effectiveness of waste water treatment for API discharges** - WWT preventative maintenance program

PLUS

- **AMR Alliance Common Manufacturing Framework:** take corrective action to address and areas that were identified and don't comply to the framework

PiE/AMR Supplier Maturity Model (3/3)

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Leading

PLUS

- **Instil 'Green' mindset**
  - Sustainability /Ethics concepts
  - Robust EHS programs, evaluated periodically for efficacy
- **Risks and opportunities for improvement identified and evaluated**
  - Audit of production and WWT as they relate to each other
  - Evaluation of water and material use in production
  - Investigating or implementing innovative solutions
- **Mass Balance -** on going review and governance to ensure API PNEC limits are not exceeded
- **Assess potential risk from sludge application to land** - Exercise appropriate duty of care for all discharges and waste streams

PLUS

- **AMR Alliance Common Manufacturing Framework:** Continued compliance to the framework and identify and implement any further areas for improvement in managing antibiotic environmental releases

Key checkpoints to ensure Water Quality

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1. **Training & awareness on Water quality/PiE/AMR topics**
2. **Demonstrating authorization/license/permit compliance**
   - Authorization/license/permit conditions
   - Wastewater treatment and monitoring
   - Permit deviations
   - Local agency reporting
   - Record keeping – WWTP parameters, equipment maintenance etc.,
3. **Characterizing wastewater discharges**
   - water balances, process flow diagrams and criteria for allowable discharge to wastewater
4. **Quantifying and assessing API discharges**
   - PNEC & PEC
   - Mass balances
   - Receiving water dilution factors
   - Analytical testing
   - API treatability - e.g. fate in a wastewater treatment plant using assessment tools such as SimpleTreat
5. **Risk Quotient <1**
   - Ensure that PEC / PNEC = Risk Quotient (RQ) RQ <1
   - Assess wastewater discharges containing APIs to determine the concentration of API (s). This predicted environmental concentration (PEC) shall be less than the predicted no-effect concentration (PNEC)

Hierarchy of control of APIs

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Reduce losses to wastewater

- Evaluate process changes that could increase yields and reduce losses
- Enhance equipment dry cleaning practices
- Redirect high API waste streams to solvent recovery, other treatment, or incineration

Collect wastewater at point of generation (POG)

- Collecting and treating (e.g. oxidation or incineration) equipment cleaning rinses

Enhance existing wastewater treatment plant

- Optimizing API reduction performance through conventional operating parameter analysis and improvement
- Improving biological solids separation through, e.g. membrane bioreactor
- Providing tertiary treatment (e.g. ozone, ultraviolet, hydrogen peroxide, Fenton's, carbon adsorption, electrochemical oxidation, membrane technologies or any suitable proven technologies)

Control of non-routine discharges

- Spills/releases: process and storage areas (e.g. tanks, container storage areas, and process sewer systems) shall be designed, constructed and operated to prevent spills or releases to the environment
- Irrigation with treated wastewater: risk assessments shall be conducted to determine potential risk from application to land (i.e. through run-off to surface water or leaching to groundwater, as well as to soil) and risks mitigated if RQ is more than 1 (RQ >1)

Good management practices

- Products shall not be directly discharged to wastewater; reject batches that cannot be recovered or reworked shall be collected for treatment on-site or off-site
- Maximize use of closed transfers between process equipment to minimize spills;
- Maximize equipment dry cleaning (vacuum, wipe) before wet cleaning; and
- Collect any dry spilled material from floors and walls before washing an area down.

Solids management program

- On-site management - demonstrate and check controls are in place for effective and safe handling, movement, storage, recycling, reuse and disposal of API containing waste
- Off-site disposal - incinerate or dispose of solid waste containing API residue to a secure landfill site.

Important steps for PiE risk minimization

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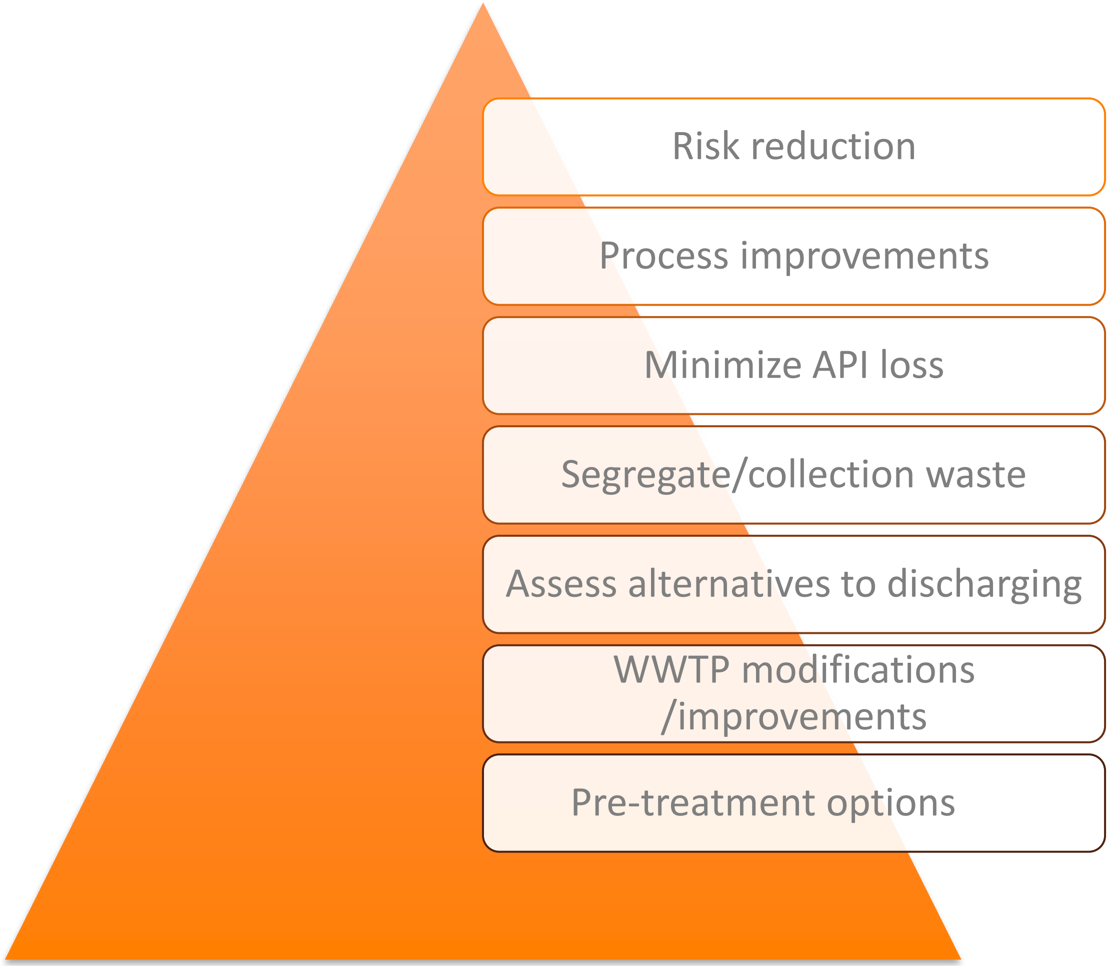
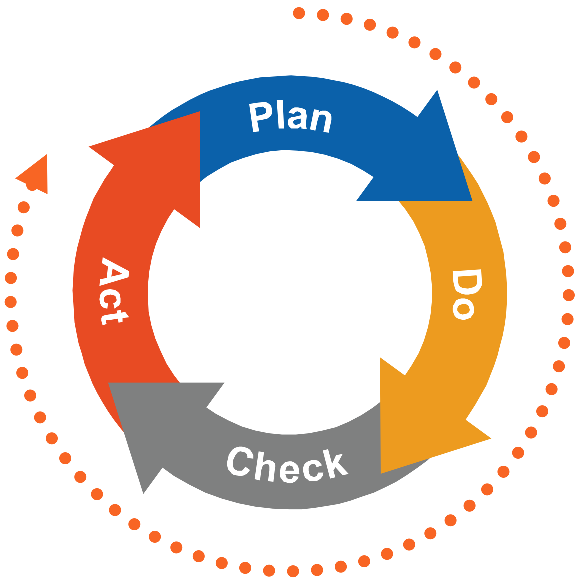


Program Auditing focus areas

1. Site visit to manufacturing areas
2. Storm water collection and retention practices/systems
3. On-site wastewater treatment plants (WWTP)
4. Waste storage areas, process and domestic wastewater collection and treatment
5. Deep wells, underground and above-ground storage tanks with associated visible piping
6. Fuel storage locations
7. Solvent storage and recovery
8. Warehouses other physical storage sheds/locations
9. Inspection of discharge locations/pollution control devices
10. Receiving stream identification and observation and fire water retention

Water Quality/PiE Program Management



Monitor and asses regulatory and industry developments, e.g. Indian effluent standard notification

Monitor overall PiE programs and performance at site and business level

- PiE as part of annual management reviews
- Prevent soil, surface water, and/or groundwater contamination

Include PiE aspects in the change management process, including scale up from development to production or when acquiring new technologies or assets

Data Transparency, e.g. PNECs for all relevant drug substances to internal and external drug substance manufacturers

Assure competent personal with clear assignment of responsibilities

Resources available to support

Resources: PSCI Website Catalogue

Categories of PSCI resources/tools available in the website:

1. General Information on PiE/Water quality
2. Anti Microbial Resistance (AMR)
3. PNEC Development
4. API Manufacturing Losses
5. API Sampling and Analysis
6. PEC and Risk Quotient (RQ) Determination
7. Risk Mitigation Management
8. Wastewater Treatment Management

Link to access:

Resources - PSCI (pscinitiative.org)

Direct links to the tools available in the PSCI website:

- SURFACE WATER PEC:PNEC CALCULATOR TOOL
- PIE & AMR EXPOSURE TOOL – SLUDGE
- PIE & AMR EXPOSURE TOOL – IRRIGATION
- PIE & AMR EXPOSURE TOOL - BANK INFILTRATION

PSCI Principles & Implementation Guidance

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The PSCI created **Industry Principles for Responsible Supply Chain Management**.

These five Principles outline our **expectations for sustainable supply chains in our industry** and provide descriptions of our expectations for pharmaceutical supply chain partners:

ETHICS · LABOR · HEALTH & SAFETY · ENVIRONMENT · MANAGEMENT SYSTEMS

To put these into practice simply, our comprehensive Implementation Guidance provides:

- ✓ **Clarity** about the Principles in each of the five areas
- ✓ A **framework** for improvement
- ✓ **Examples** of how to meet the PSCI expectations

www.pscinitative.org

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Q&A

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Thank you for joining us for Musi river wastewater workshop in Hyderabad, India

We look forward to seeing you again

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About the secretariat
Carnstone Partners Ltd is an independent management consultancy, specialising in corporate responsibility and sustainability, with a long track record in running industry groups.

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