PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Building responsible supply chains

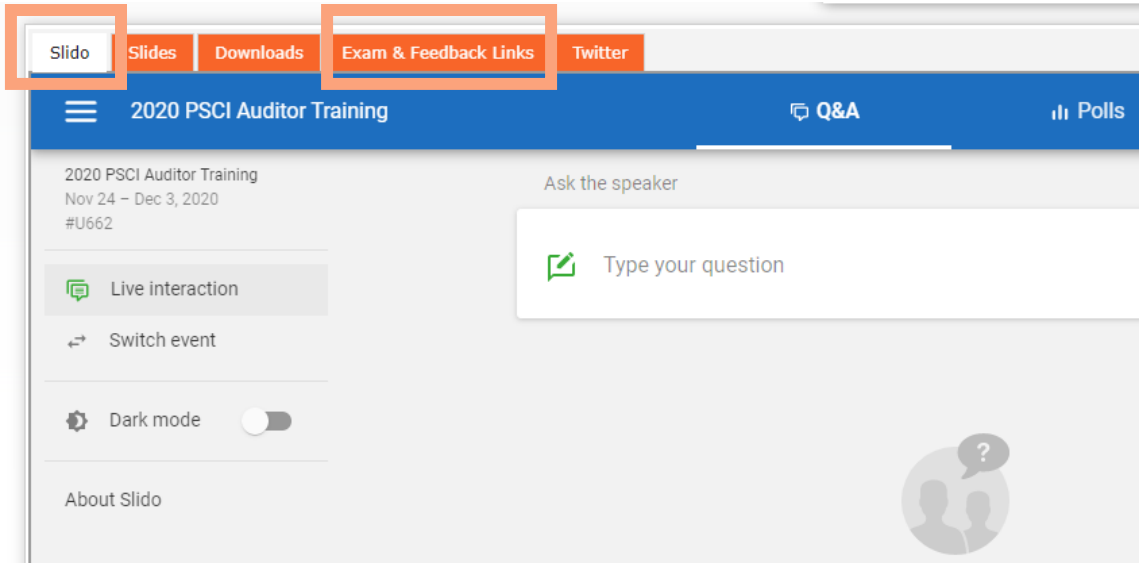
PSCI Auditor Training 2020

Day 2 Environmental Protection; PiE and AMR

25 Nov 2020

Practicalities

- Switch to audio feed only for better connection. Chinese attendees click at Live Stream (China)
- Break
- We'll be using Slido for Q&As, please click Slido tab to enter your questions or go to https://www.sli.do/ to pose questions with the code **#U662**
- Exam
- Certificates
- Feedback survey



Anti-Trust Statement

While some activities among competitors are both legal and beneficial to the industry, group activities of competitors are inherently suspect under the antitrust/anti-competition laws of the US, UK and other countries in which our companies do business. Agreements between or among competitors need not be formal to raise questions under antitrust laws, but may include any kind of understanding, formal or informal, secretive or public, under which each of the participants can reasonably expect that another will follow a particular course of action or conduct. Each of the participants in this meeting is responsible for seeing that topics which may give an appearance of an agreement that would violate the antitrust laws are not discussed. It is the responsibility of each participant in the first instance to avoid raising improper subjects for discussion, such as those identified below.

It is the sole purpose of this meeting to provide a forum for expression of various points of view on topics described in the agenda and participants should adhere to that agenda. Under no circumstances shall this meeting be used as a means for competing companies to reach any understanding, expressed or implied, which tends to restrict competition, or in any way to impair the ability of members to exercise independent business judgment regarding matters affecting competition.

Topics of discussion that should be specifically avoided are:

i. Price fixing;
ii. Product discounts, rebates, pricing policies, levels of production or sales and marketing terms customer and territorial allocation;
iii. Standards setting (when its purpose is to limit the availability and selection of products, limit competition, restrict entry into an industry, inhibit innovation or inhibit the ability of competitors to compete);
iv. Codes of ethics administered in a way that could inhibit or restrict competition;
v. Group boycotts;
vi. Validity of patents;
vii. On-going litigation;
viii. Specific R&D, sales or marketing activities or plans, or confidential product, product development, production or testing strategies or other proprietary knowledge or information.

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

Environmental Protection - PiE

Growing environmental issues of pharmaceuticals in the environment and insights of audit findings

Manjit Singh
Associate Director- Corporate Sustainability
Centrient Pharmaceuticals India Pvt Ltd.

Speaker Bio

Name: Manjit Singh

Title: Associate Director- Corporate Sustainability

Organization: Centrient Pharmaceuticals India Pvt Ltd.

Organization Profile: Centrient is headquartered in The Netherlands. Centrient started operations in 1869. Centrient is pioneer and leader in penicillin, penicillin-based antibiotics and statins.

Manjit has about 32 years' experience in pharmaceutical mfg operations. Responsible for global sustainability in operations. He is Centrient lead for PSCI and PSCI lead for India.
He is bachelor in chemistry from Punjabi University, Patiala.
Post Graduate Diploma in Operations, Indira Gandhi National Open University, Delhi.

Growing environmental issues of pharmaceuticals in the environment and insights of audit findings

Understanding Pharmaceuticals in Environment (PiE)

Pharmaceutical level in Water

Tools and Techniques to Tackle PiE

Zero Liquid Discharge Wastewater Treatment

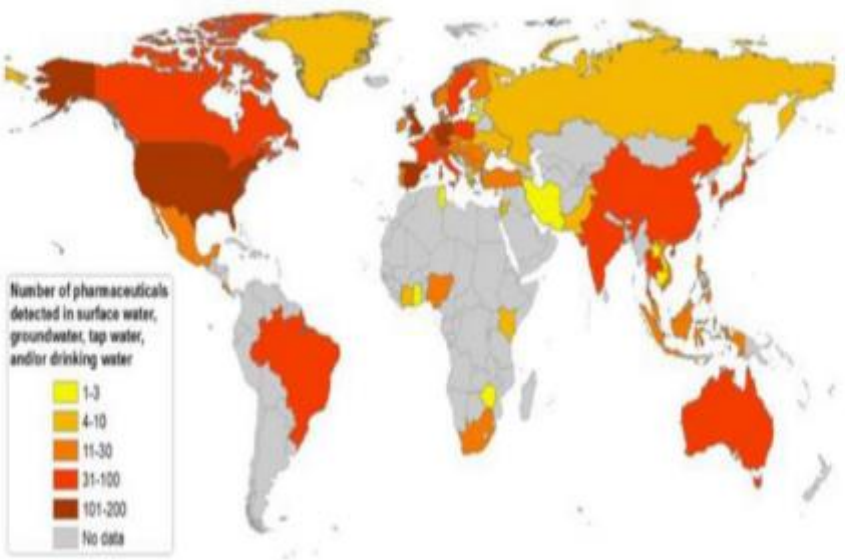
PSCI environment principles , audit insights and SAQ.

Understanding Pharmaceutical in Environment (PiE)

- Medicines have played a major role in increasing human life expectancy.
- Since 1980's HIV deaths have fallen by 80% and since 1990's deaths from cancer have fallen by 20% due to the innovation in medical sector and availability of medicines.
- One of the unintended but inevitable results of delivering the life-changing medicines to patients is that our products can find their way into the environment.
- Reports of active pharmaceutical ingredients (APIs) in surface water from manufacturing in EU, USA, India, and elsewhere indicate concentrations have reached to unacceptable limits of mg/L in some cases.
- Though scientific evidences provide little information on real environmental impacts which may me attributable to the presence of pharmaceuticals, the long-term environmental impact of man-made substances cannot be ignored, including medicines
- Also, one of the subtopic under PiE is antimicrobial resistance (AMR) which has a significant negative impact and if it is not addressed could lead to serious consequences.

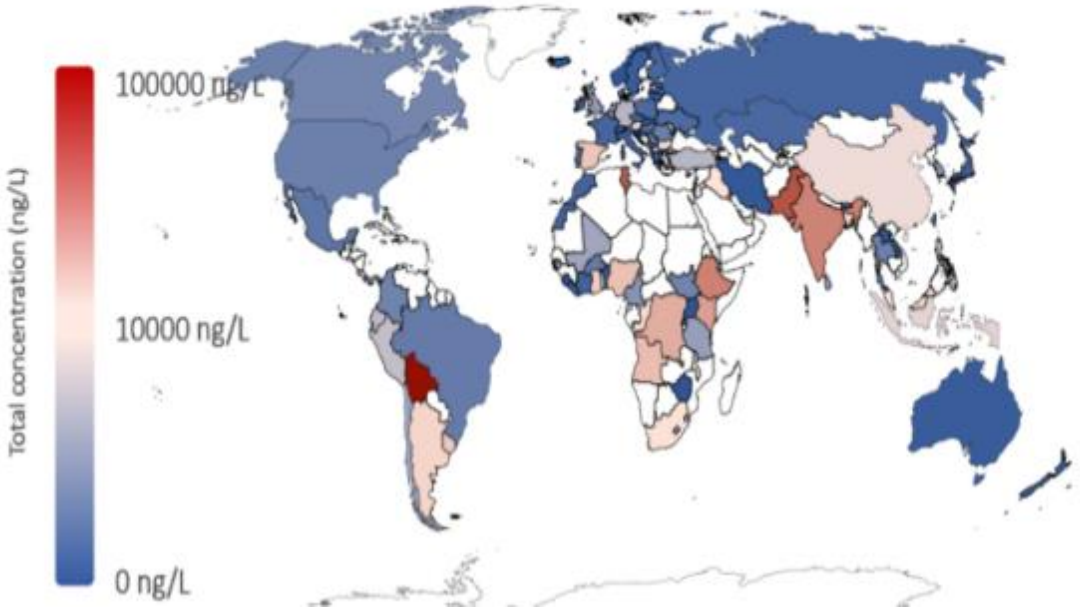
Pharmaceuticals Level in Water

Measurements of pharmaceuticals in river waters



Aus der Beek et al., 2016

Total concentrations by country



Source:
aus der Beek, T. et al. (2016), "Pharmaceuticals in the environment-Global occurrences and perspectives", Environmental Toxicology and Chemistry, Vol. 35/4, pp. 823-835, http://dx.doi.org/10.1002/

Most Present PiE

Substance	Therapeutic group	Africa	Asia-Pacific	EEG	GRULAC	WEOG	Global
Diclofenac	Analgesics	3	8	13	3	23	50
Carbamazepine	Antiepileptics	3	6	13	2	24	48
Ibuprofen	Analgesics	3	8	10	2	24	47
Sulfamethoxazole	Antibiotics	5	9	10	2	21	47
Naproxen	Analgesics	2	8	10	2	23	45
Estrone	Estrogens	1	10	6	2	16	35
Estradiol	Estrogens	2	9	4	2	17	34
Ethinylestradiol	Estrogens	1	8	3	2	17	31
Trimethoprim	Antibiotics	2	9	3	2	13	29
Paracetamol	Analgesics	1	6	4	3	15	29
Clofibric acid	Lipid-lowering drugs	1	3	5	2	12	23
Ciprofloxacin	Antibiotics	1	5	1	2	11	20
Ofloxacin	Antibiotics	1	4	1	1	9	16

These substances are the only ones that have been found in each region.

EEG = eastern Europe;
GRULAC = Latin America and Caribbean;
WEOG = western Europe and others.

Source:
aus der Beek, T. et al. (2016), "Pharmaceuticals in the environment-Global occurrences and perspectives", Environmental Toxicology and Chemistry, Vol. 35/4, pp. 823-835, http://dx.doi.org/10.1002/

Sharp Decline of Vulture Population in Asia

The rapid decline in vulture populations was first reported in the late 1990's by Dr. Vibhu Prakash of the Bombay Natural History Society. The decline was quick and severe and posed a problem in a part of the world that relied heavily on the ubiquitous vultures for the efficient disposal of dead livestock. Eighty-five percent showed evidence of acute kidney failure. The scientists tested the vulture tissue for traces of heavy metals, pesticides and other chemicals, found none. Further investigation established residues of diclofenac in dead vultures. The researchers then conducted experiments that corroborated that the amount of diclofenac a vulture might ingest from a carcass could kill it within days. The veterinary use of diclofenac is banned in and formulation vial limited to 3 ml.

PiE – Concern to Industry and Regulators

PiE was first discussed as concern by the USEPA in 2005. It developed a list of Priority Compounds which included

Eco-Pharmaco-Stewardship:

The Inter-Association Initiative on Pharmaceuticals in the Environment (IAI PIE) combines the expertise of the Association of the European Self-Medication Industry (AESGP), the European Federation of Pharmaceutical Industries and Associations (EFPIA), and the European Generic and Biosimilar medicines association (EGA) developed Eco-Pharmaco-Stewardship (EPS) initiative.
It considers the entire life-cycle of the medicine and addresses the roles and responsibilities of the pharmaceuticals industry, environmental experts, doctors, pharmacists, and patients.

OECD
BETTER POLICIES FOR BETTER LIVES

A combination of promoting hygiene practices to reduce the incidence of infection and disease, encouraging sustainable pharmaceutical design and production, spreading awareness of responsible pharmaceutical use and disposal, and improving environmental monitoring and risk assessment of pharmaceuticals, are critical steps to achieving the dual sustainable development goals of improving health and protecting the environment." Rodolfo Lacy Director of the Environment Directorate, OECD

Tools & Techniques to Tackle PiE

Environmental Risk Assessment (ERA)
It examines potential risks of a medicinal substance for the environment and ensures that adequate precautions are in place where specific risks are identified. Since 2006, marketing authorizations applications include ERA in EU

Traditional Wastewater Treatment :
The treatment technique applies a combination of primary, secondary (biological) and tertiary treatment based on the effluent matrix. The treated water is discharged to water bodies or/ and irrigation. Sometimes partially recycled.

Common Antibiotic Manufacturing Framework by AMR IA : For antibiotic manufacturers AMR Industry Alliance has released a guiding document setting minimum requirements for reducing the risk of AMR through manufacturing.

Zero Liquid Discharge (ZLD) :
ZLD is the process of treating wastewater through inhouse WWTP and then using the treated water back to utilities& other use, it is prevalent India and China

Overview ZLD : Design & Process

ZLD refer to the installations of facilities and system which enables absolute recycling (100%) of treated water. ZLD is qualified based on performance i.e. water generated and recycled. No use for horticulture, irrigation and no discharge to water bodies. Solids waste or salts generated to be utilized or landfill.

Mfg Plant

High TDS

Low TDS Effluent

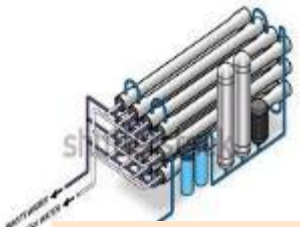
Stripper & MEE

Agitated Thin Film Dryer

Salt for landfill and coprocessing.

Biological Treatment

Ultra Fiilteration



Reverse Osmosis

Treated Water

Cooling Tower

Feed for boiler

Other use (washings /toilets/ Fire Fighting)

PSCI Principles to Protect- Environment

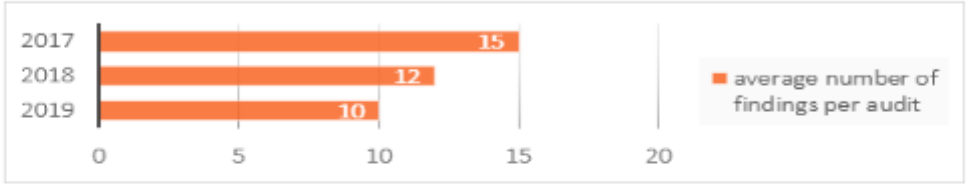
Suppliers shall operate in an environmentally responsible and efficient manner to minimize adverse impacts on the environment. Suppliers are encouraged to conserve natural resources, to avoid the use of hazardous materials where possible and to engage in activities that reuse and recycle. The Environmental elements include:

WASTE AND EMISSIONS
Suppliers shall have systems in place to ensure the safe handling, movement, storage, disposal, recycling, reuse, or management of waste, air emissions and wastewater discharges. Any waste, wastewater or emissions with the potential to adversely impact human or environmental health shall be appropriately managed, controlled and treated prior to release into the environment. This includes managing releases of active pharmaceuticals into the environment (PiE).

PSCI- Audit Insights

Audit Findings Analysis (2017-2019)

- Average number of findings per audit tends to decrease over the years.
- H&S has always been the area with most findings, which occupies over 50% of the findings in 2019, followed by Management System and Environment.
- The presence of Environment findings has been growing over the past three years.
- Percentage of Labor and Ethics findings are going down annually, together consist of 8% of findings in 2019 - reasons behind this could include increased number of HSE audits, qualifications of auditors etc.



Audit Insights

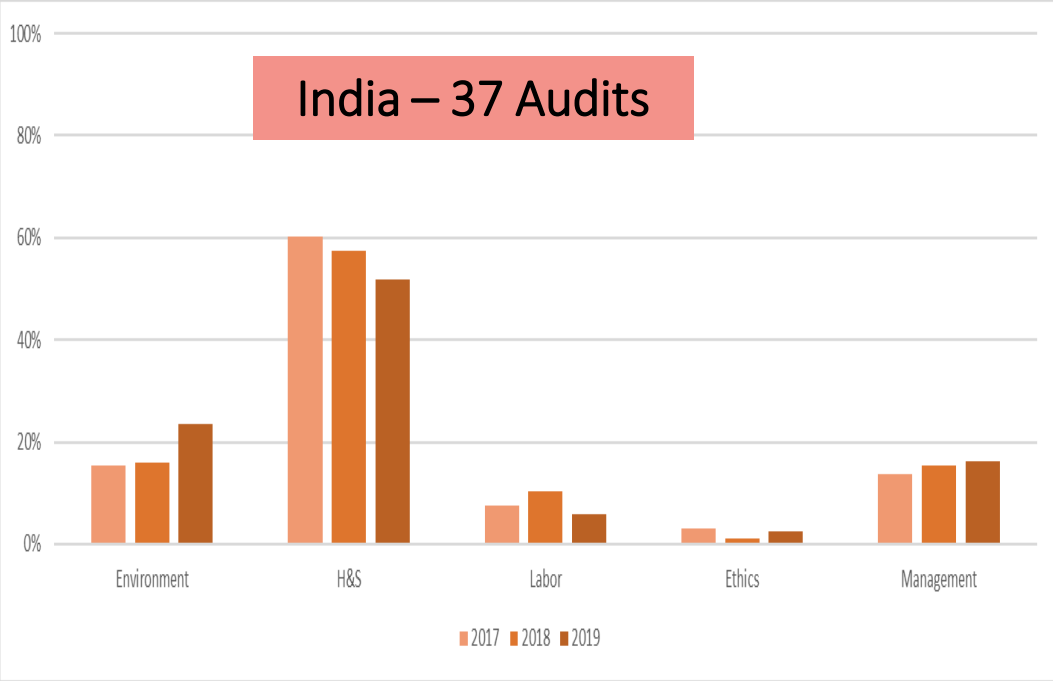
Audit Findings Analysis (2018-2019)

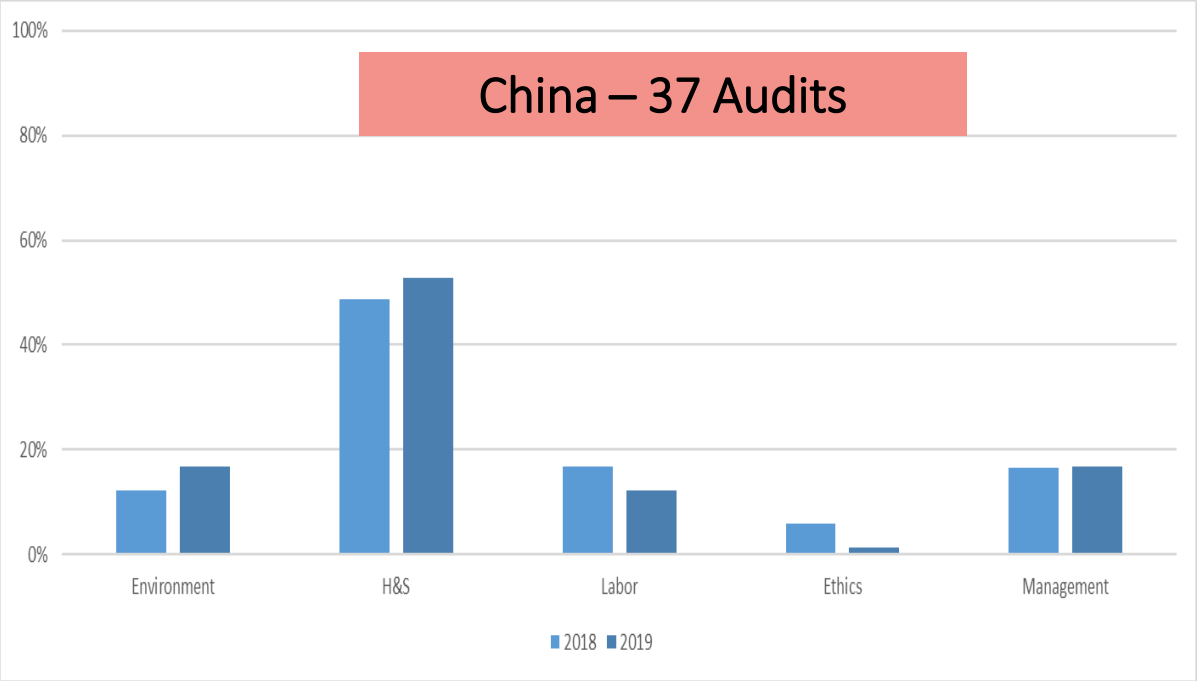
- Over 70% of the findings are found in **API, Chemical and Finished Formulations suppliers**, half of them are from **China and India** (2018-2019).
- Topics/subclauses with most findings:
  - **H&S:** exposure risk & communication, hazard analysis, pallet racking related, safety work permit
  - **Environment:** spill control, API in wastewater, waste management
  - **Management System:** business continuity planning, supplier evaluation, regulatory compliance
  - **Labor:** wages, benefits & working hours, freely chosen labor
  - **Ethics:** Business Integrity & Fair Competition

- Around 1% of total findings are critical findings every year.
- Critical findings are found in H&S, Environment and Labor in the past two years, but not in Ethics and Management System.

Finding classification	2017	2018	2019
Critical*	1%	1%	1%
Major	4%	16%	14%
Minor	2%	22%	44%
Other	92%	61%	42%

High Level Findings – India & China





PSCI - SAQ Encompass PiE

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.	Disposal method	Off-site	On-site	Yes No Comments **AUDITOR GUIDANCE**
		Incineration	With energy recovery Without energy recovery Both Please explain:	With energy recovery Without energy recovery Both Please explain:	Yes No Comments **AUDITOR GUIDANCE**
		Landfill	If so, is the landfill area hermetically sealed? Please explain:	If so, is the landfill area hermetically sealed? Please explain:	Yes No Comments **AUDITOR GUIDANCE**
		Deep Well	Please explain:	Please explain:	Yes No Comments
		Land Application (i.e. Wastewater sludge, biomass from fermentation, wastewater (i.e. irrigation) methods)	Please explain:	Please explain:	Yes No Comments

SAQ Guidance is a Powerful Compass

1. (Q38, Disposal Method)

Review in detail treated wastewater and/or sludge/fermentation biomass applied to land for irrigation and/or fertilizing purposes that might include API residual.

2. (Q38, Incineration)

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

b) 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?
- Are environmental impacts from API residuals considered?
- Describe all wastes that contain API that are destroyed by incineration (i.e., mother liquors, rinsate from bulk containers, rinsate from production, bulk containers, packaging waste, off spec product, etc.)

c) Describe the incineration process(es) used for these wastes.

d) If branded product or packaging destroyed by incineration, what sample records were reviewed to confirm disposal? Have audits been performed of transportation firms and disposal sites?

3. (Q38, Landfill)

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

b) 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?
- Are environmental impacts from API residuals considered?
- Which wastes contain API (bulk containers, rinsate from bulk containers, rinsate from production, packaging waste, off spec product, etc.)? Describe how waste is destroyed (incineration or energy recover).
- Describe how APIs are quantified in different types of waste (Sludge, Biomass etc.) : 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.

c) How is branded product or packaging destroyed? Which sample records were reviewed to confirm? Have audits been performed of transportation firms and disposal sites?

PSCI - SAQ Encompass PiE

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	Yes No Comments AUDITOR GUIDANCE

- **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)**

Guidance for the Auditors

- Understand the menace of pharmaceutical pollution in the region.
- Watch environment policy , standard operating procedure specific to wastewater, wastewater permission and compliance.
- Investigate for preventive approach like Environment Risk Assessment, key risks and mitigation.
- Training of the people responsible w.r.t. PiE and AMR.
- Make a round of wastewater treatment plant, understand the technology, Infrastructure, capacity vs inflow/day , disposal of liquid and solid waste.
- Investigate the claim of ZLD by evidence of water balance volume / day i.e. water extraction, inflow to WWTP, breakdown history, treatment, quality parameters vs specifications of treated water (preferably see physical sample) and recycling volume . Base your ZLD performance argument on water balance i.e. the losses, water recycled and alternative measure in case of breakdown.
- Investigate the claim of PEC/PNEC determination based on the methodology deployed i.e. mass balance or analysis. Refer to the PSCI mass balance tool and validation of the analytical method and sampling technique. You may refer to the PNEC table published by IA.
- Frequency of determining the PEC and PNEC.

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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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PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

Stormwater: Issues and best practice

Dr. Daniel Rehm
Lead HSE Advisor Elanco External Manufacturing (EEM) API and EMEA
Elanco Animal Health Inc.

Speaker Bio

- Daniel is Lead HSE Advisor in the Elanco External Manufacturing EMEA &API Hub Basel, Switzerland
- PhD in Chemistry from Humboldt University in Berlin, Germany with 16 years of experience in Chemical Industry, Insurance and Pharmaceutical Industry. Functional experience in R&D, HSE, Engineering and Manufacturing
- Working in Elanco for 5 year.
- Additional work as Loss Prevention Manager and Tech Transfer Project Lead
- Team lead of the PSM sub-team of the PSCI Capability Committee

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Agenda

Stormwater: what issued can be found

Potential pollution sources of stormwater

Stormwater pollution prevention

Zero Liquid Discharge ETP

Agenda

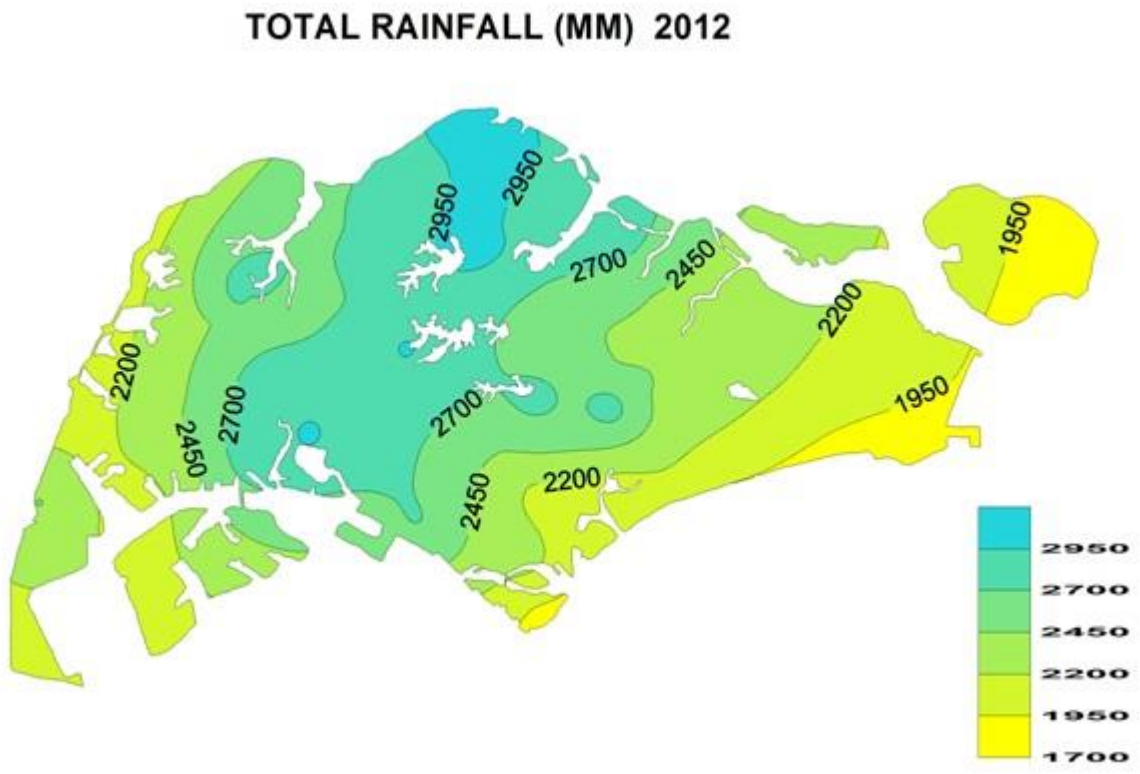
1. Stormwater: what issued can be found
2. Potential pollution sources of stormwater
3. Stormwater pollution prevention

Stormwater: personal experience

- November 1st, 1986: Schweizerhalle fire, contaminated fire water
- 2006 to 2009: Singapore: strict management of stormwater
- June 15th, 2015: tropical storm Bill in Houston, USA

Rain in Singapore

Up to 3000
mm per year



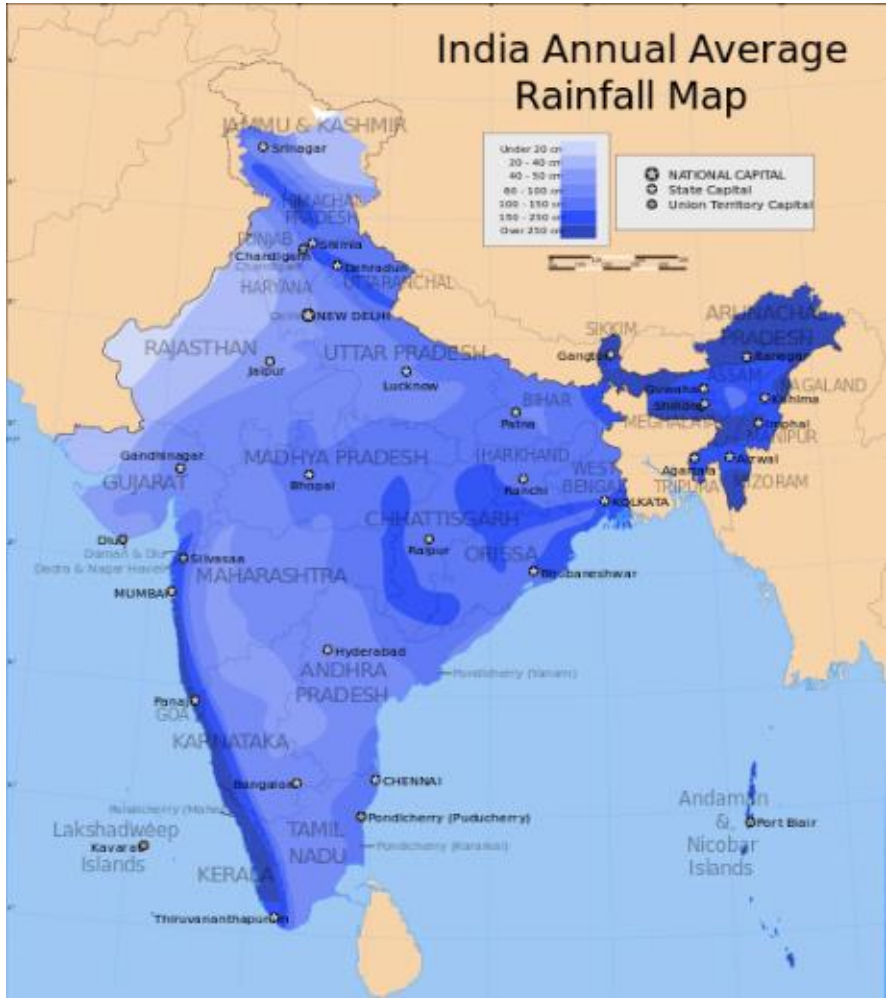
Source: National Environment Agency Singapore

Stormwater management In Singapore

- Water is seen as a valuable resource in Singapore
- Very strong regulation on stormwater management
- Chemical and pharmaceutical industry has to implement strict control of stormwater release

Rain in India

Up to 2500
mm per year



Source: Wikipedia

What Is Stormwater Runoff?

Stormwater runoff is water from rain or snowmelt that does not immediately infiltrate into the ground and flows over or through natural or man-made storage or conveyance systems.

What Are Its Impacts?

Runoff from areas where industrial activities occur can contain toxic pollutants (e.g., heavy metals and organic chemicals) and other pollutants such as trash, debris, and oil and grease, when facility practices allow exposure of industrial materials to stormwater. This increased flow and pollutant load can impair waterbodies, degrade biological habitats, pollute drinking water sources, and cause flooding and hydrologic changes to the receiving water, such as channel erosion.

Types of activities at industrial facilities with potential of pollution in stormwater

- Loading/unloading operations
- Outdoor storage
- Outdoor process activities
- Dust or particulate generating processes
- Illicit connections and non-stormwater discharges
- Waste management

Examples

Stormwater pollution: Loading/unloading operations

- Incomplete bunding
- No spill retention capacity

Stormwater pollution: Outdoor storage

- No secondary containment for outdoor storage of material

Stormwater pollution: Outdoor process activities

- Open structure building without sufficient retention capabilities

Stormwater pollution
Dust or particulate generating processes

- Insufficient capacity or no dust filters

- Ashes from coal fed boilers and/or stacks

Stormwater pollution: Illicit connections and non-stormwater discharges

- Overflow of waste water tanks
- Leakage from cooling towers with contaminated water (recycled from waste water treatment plant

Stormwater pollution: Waste management

- Storage of hazardous waste without bunding or secondary containment

Stormwater pollution prevention: 4 steps

- Step 1: Form a team of qualified personnel
- Step 2: Assess potential stormwater pollution sources
- Step 3: Select appropriate control measures
- Step 4: Inspection and monitoring of controls

Form a team of qualified personnel

- The team should consist of those people on-site who are most familiar with the facility and its operations
- Team should consist ideally of members from the following departments:
  - HSE
  - Engineering
  - Effluent treatment operators

Assess potential stormwater pollution sources

- Assess the different pathways how storm water can be contaminated
  - Mass balance of API process
  - Fate of water from equipment washing

- Site tours to identify gaps

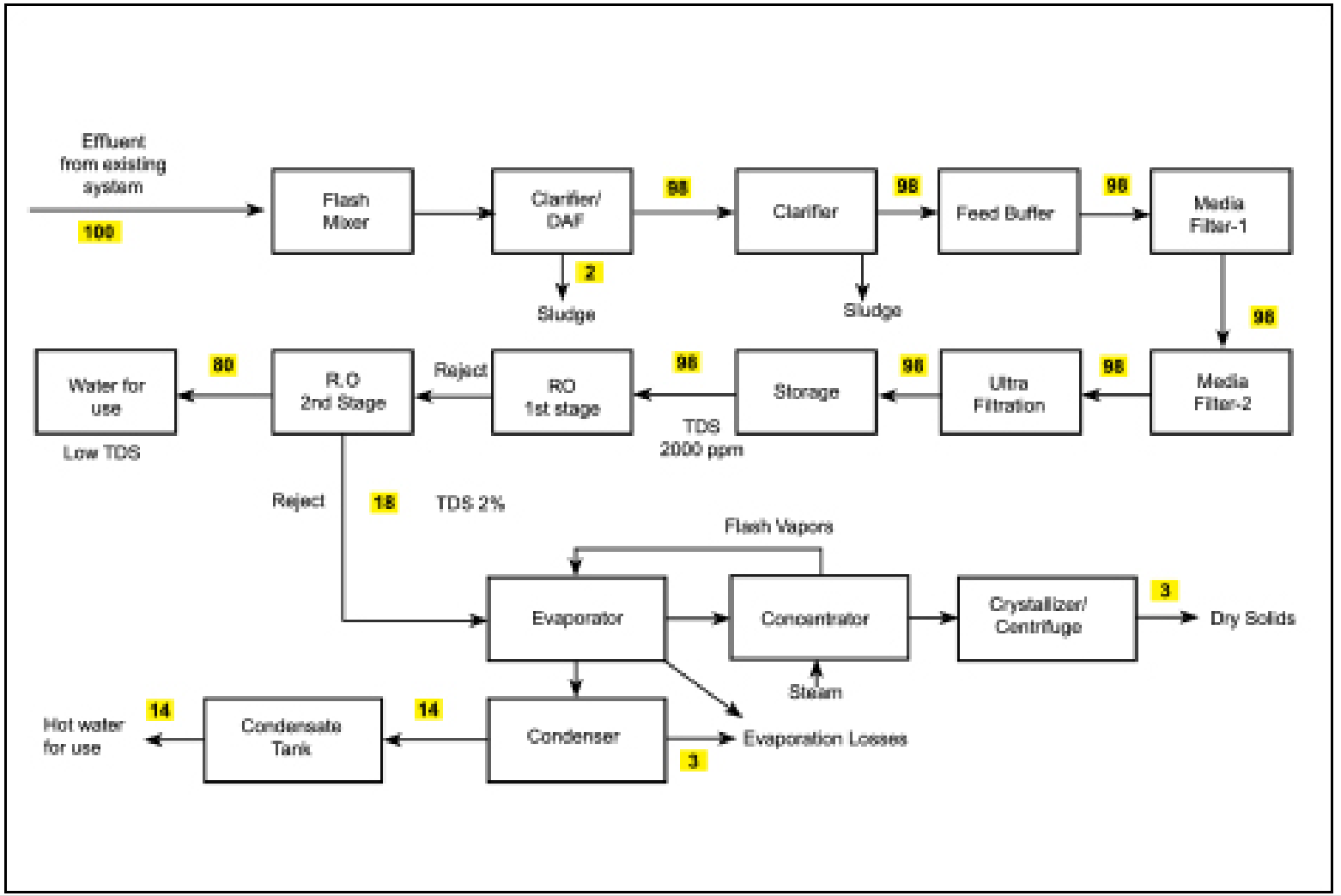
Select appropriate control measures

- Hierarchy of control measures
  - Eliminate
  - Reduce
  - Mitigate
- Engineering controls preferable over administrative controls
- Analysis of all stormwater before release

Inspection and monitoring of controls

- Regular site tours to control controls and identify new issues
- Regular training of personnel about stormwater control
- Continuous improvement mind set needed to guarantee future success

ZLD ETP What to look for....



Zero is not always zero...

- Check the mass balance
- Onsite inspection of water flows (check for staining, wet areas etc.)
- Ask for the transport of salt residues (to where, how etc.)
- Inspect salt storage areas
- Ask for stormwater managment

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About the Secretariat
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BREAK

It is break now. Please come back in 10 minutes.

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Building responsible supply chains

Introduction to PiE and AMR

Dr Paul Barnett

Director

Environment Health & Safety

GlaxoSmithKline

Speaker Bio

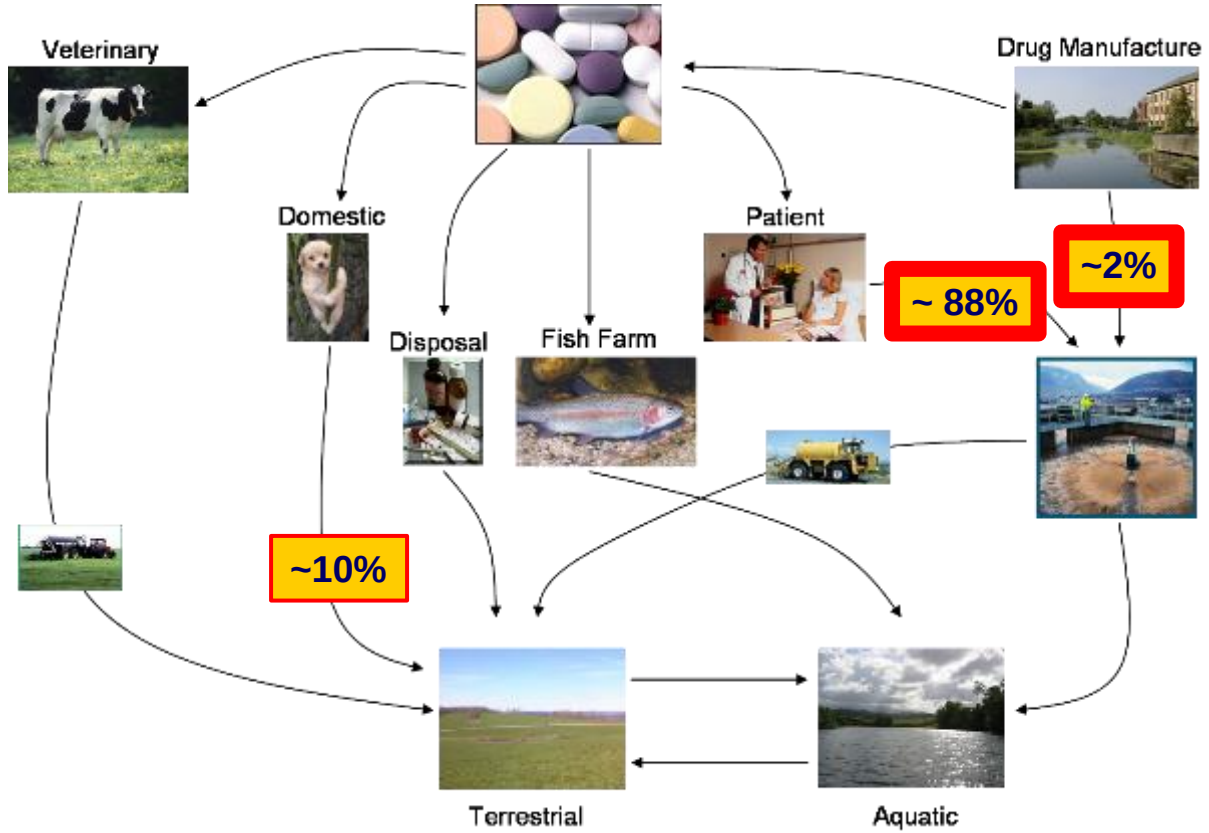
Paul Barnett BSc PhD PMP

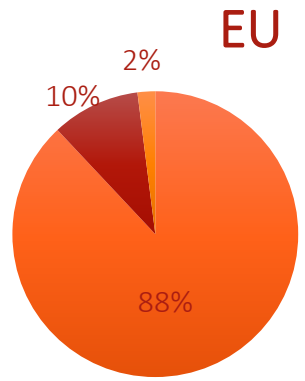
Director, Environment, Health & Safety

- 32 years consumer healthcare and pharmaceutical experience in GSK, including roles in Oral Health and Smoking Cessation R&D, managing new product launches and leading GSK's environmental sustainability initiatives
- Currently leading GSK's AMR program to ensure GSK's supply chain manufacturing sites are compliant with the AMR Alliance Manufacturing framework and discharge targets by the end of 2021
- PhD in cancer research (University of London)
- Project Management Professional (PMP).

Sources of Pharmaceuticals in the Environment

Three routes into the Environment





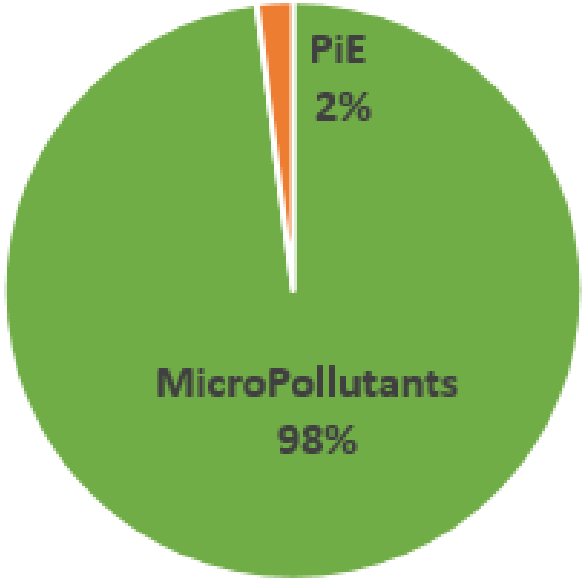
Environmental concentrations µg/L – ng/L (PPB-PPT)

Release estimates from BIO-IS Report (2013)

PiE – An Overview

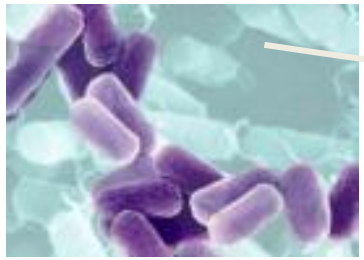
Most pharmaceutical are unlikely to be a risk to the environment

- Pharmaceuticals are widespread in the environment: µg/L (PPB) – ng/L (PPT)
  - Surface water and ground water (rivers, lakes, marine)
  - Drinking water
  - Soil and sediment (agricultural land)
- Pharmaceuticals are a subset of 'micro pollutants' (~100,000): industrial chemicals, household products, detergents, pesticides, insecticides, biocides, caffeine, recreational drugs etc etc.
- Pharmaceuticals have demonstrable health benefits to people which is recognised by regulatory bodies
- Data so far suggests that pharmaceuticals generally are unlikely to be a risk for human health or the environment.
- However, Industry acknowledges there are concerns around PIE and seeks to address these in a scientifically robust manner.

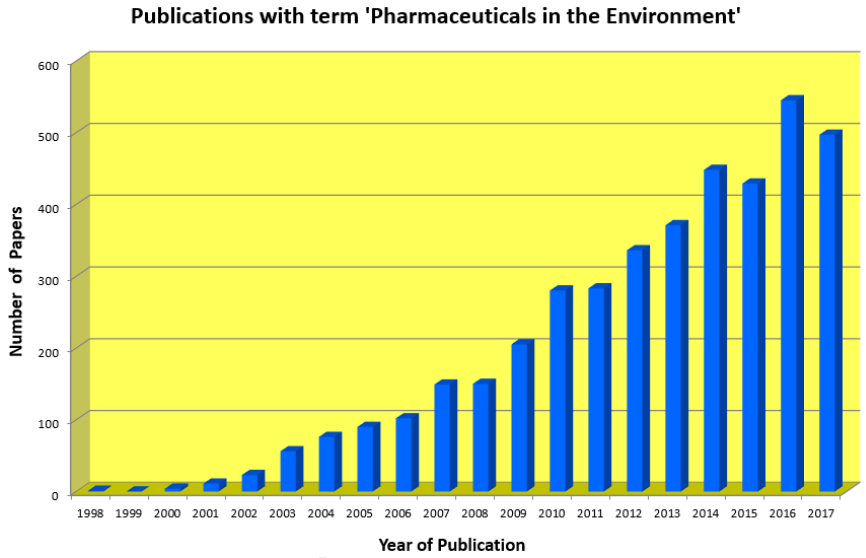


PiE – Identified Areas of Concern

- Endocrine disrupting Chemicals (EDC)
  - Feminisation of fish from exposure to EDCs.
  - Source: Natural and synthetic estrogenic hormones
  - Lab studies: potential for reproductive effects at environmental concentrations.
- Diclofenac
  - Decimation of vulture population on Indian sub-continent.
  - Strong correlation with veterinary use of diclofenac in cattle.
  - Atypical exposure scenario. Conflation of culture, animal husbandry and unregulated use of veterinary medicine.
- Antimicrobial resistance (AMR)
  - Widespread use of antibiotics: emergence of antibiotic resistant strains e.g. MRSA, MDR-TB etc.
  - Antibiotic resistance genes have their origins in environmental bacteria. The role of antibiotic residues (PiE) in the environment on AMR is uncertain

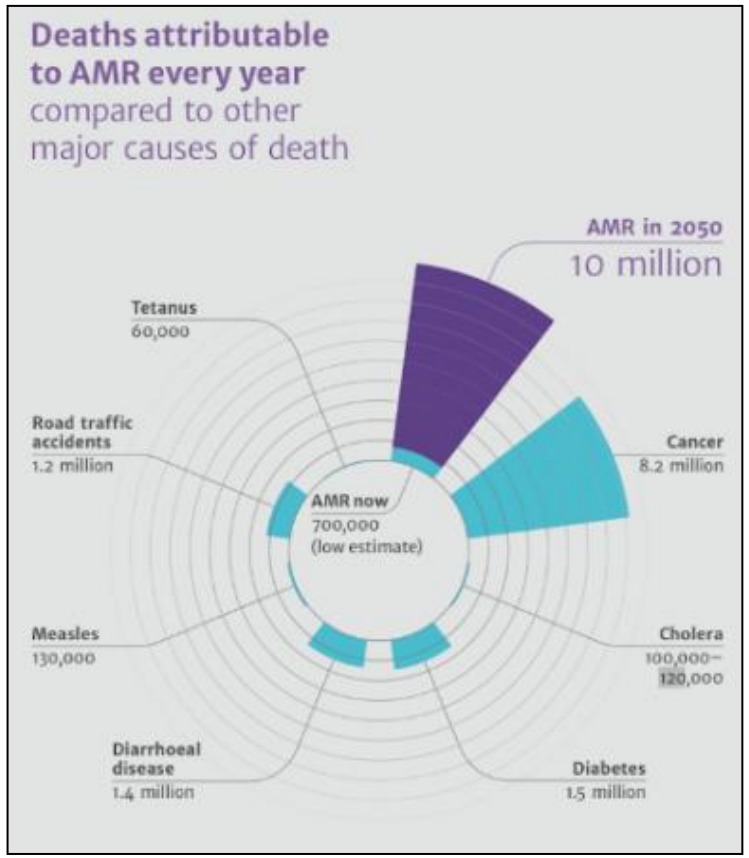


PiE in Scientific Literature



Antimicrobial Resistance (AMR)

A Threat to Global Healthcare



Without effective action on AMR it is estimated that 10 million people will die annually by 2050 with a concomitant loss of $100 Trillion to the global economy.

Jim O'Neill, 2014

https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf

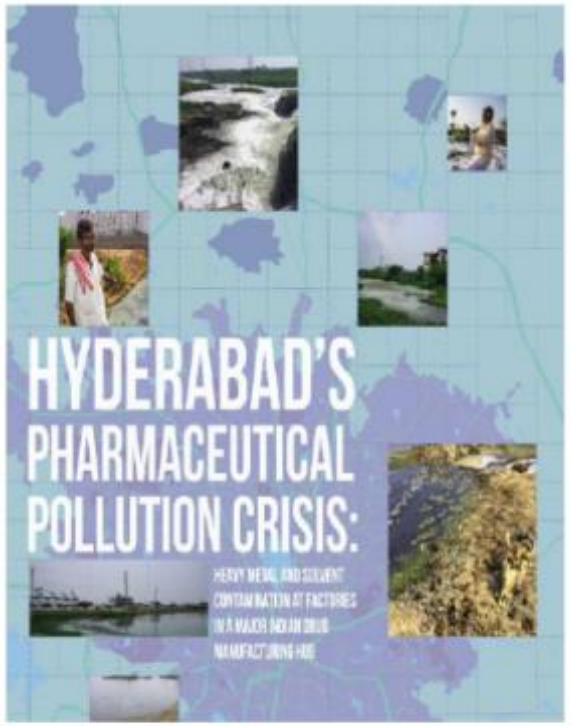
Call To Action

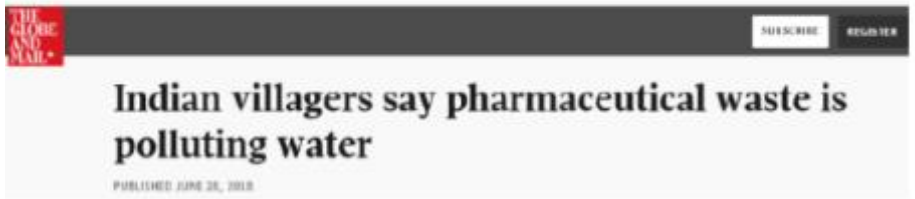
- 2015 World Health Assembly (WHA) endorsed global action plan to tackle AMR; urged Member States to develop national action plans (NAPs) aligned with objectives of global action plan
- 2015 UN recognizes important of tackling AMR to achieving sustainable Development Goals
- 2016 –O'Neil report (UK) "to analyse global problem of rising drug resistance and action pose concrete actions to tackle it internationally". Viewed as a key report, often cited
- September 2016: 13 international pharmaceutical companies including GSK, committed to the UNGA roadmap to combat AMR
- By 2018 almost all country national action plans in place (approved or in development)
- 2020 –several articles concerning widespread antibiotic use to treat covid patients may increase AMR risk

Development of Bacterial Resistance AMR

- Antimicrobial resistance is a natural phenomenon resulting from evolutionary selective pressure
- In the presence of an antibiotic, all the susceptible bacteria die, allowing drug resistant bacteria to proliferate
- Antibiotic resistance can occur through various mechanisms
- Bacteria can transmit resistance genes via small cellular elements called plasmids; mobile elements which can transfer genetic material between bacteria
- Today, Gram-negative pathogens are becoming resistant to nearly all antibiotics currently available
- More recently, the environment is seen as an important reservoir of antimicrobial resistance

Stakeholder reports include manufacturing discharges as a pollution/AMR risk

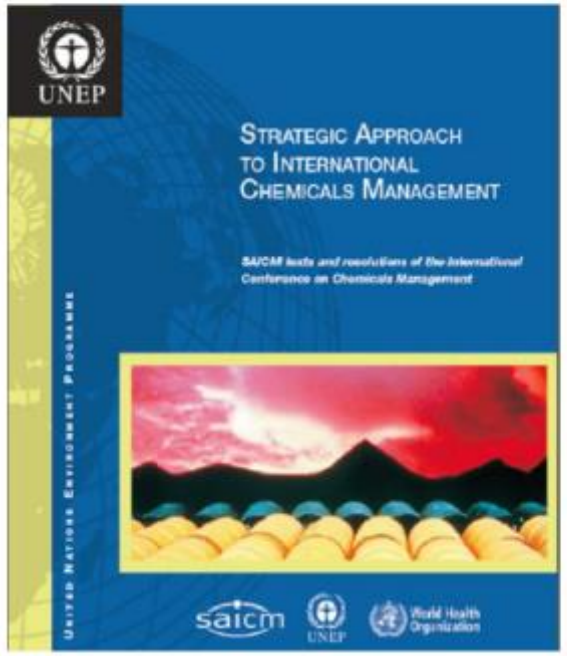




Big Pharma's Pollution is Creating Deadly Superbugs While the World Looks the Other Way

Bureau of Investigative Journalism 6 May 2017

…including calls for Governments to act on environmental risk



SAICM: UNEP proposes persistent pharmaceutical as a new, emerging policy issue in 2015

Represenatives call for action on antibiotic resistance

Members of Congress are calling on the FDA to do its part in curbing antibiotic resistance by helping hold pharma companies responsible for pollution. It's been reported that drug manufacturers in India will sometimes dump antibiotics into surrounding waters, which can encourage the development and spread of drug-resistant bacteria. Representatives Louise Slaughter (D-NY), Peter DeFazio (D-OR), and Carol Shea-Porter (D-NH) have sent the FDA a letter urging the agency to work with its regulatory counterparts in those countries to make sure they're taking action. "Bacteria have no respect for national borders," they warn. "China and India's [problems] today can easily become our problems tomorrow

StatNews May 2017

India may formulate standards for pharma antibiotic residue

Hindustan Times July 2018

European Union Strategic Approach to Pharmaceuticals in the Environment (March 2019)

8

…including calls for Governments to act on environmental risk

AMR Industry Alliance

life sciences industry response to call for action

one of largest private sector coalitions established to provide sustainable solutions to AMR crisis.

members committed to keeping antibiotics effective & promoting innovation by contributing to, and measuring their efforts in, four key areas:

Research; appropriate use; access; responsible manufacturing

drive progress, grow membership - bold set of shared goals, commitments, effective stakeholder communication

https://www.amrindustryalliance.org/why-the-amr-industry-alliance/

AMR Industry Alliance: Manufacturing Commitments

The signatory companies of the AMR Industry Alliance, have committed to measures to reduce the environmental footprint from the production of antibiotics. Specifically;

i. Review our own manufacturing and supply chains to assess good practice in controlling releases of antibiotics into the environment.

ii. Establish common framework for managing antibiotic discharge, and start to apply it across our own manufacturing and supply chain

iii. Work with stakeholders to develop a practical mechanism to transparently demonstrate that our supply chains meet the standards in the framework.

iv. Work with independent technical experts to establish science-driven, risk-based targets for discharge concentrations for antibiotics and good practice methods to reduce environmental impact of manufacturing discharges

amr INDUSTRY ALLIANCE

Research-based companies:

Boehringer Ingelheim, gsk, Johnson & Johnson, SHIONOGI, MSD, Pfizer, Roche, SANOFI, Otsuka, Sumitomo Dainippon Pharma

Generics companies:

ATHLONE LABORATORIES, AUROBINDO, CENTRIENT, teva, Mylan, NGB, NOVARTIS, Recipharm

AMR Industry Alliance Manufacturing WG Members 14th October 2019

AMR Industry Alliance: Manufacturing Commitments

Alliance Framework

Common Antibiotic Manufacturing Framework:

- Published 2018
- Requirements & methodology to conduct risk evaluation to effectively manage /minimize potential environmental release of antibiotics from manufacturing operations
- Designed to ensure that manufacturing sites (and **especially third-party supplier sites**) are, and are seen to be, managing antibiotic production and associated waste streams responsibly (much stakeholder attention here!)
- Codifies what should be regarded as good practice
- **Adherence to framework drives selection and use of appropriate suppliers**

WWW.AMRINDUSTRYALLIANCE.ORG

Management of Antibiotic Discharges from Manufacturing: Setting Wastewater Discharge Targets

- **PNEC (Predicted No Effect Concentration): the concentration of a substance in a receiving water body that is not expected to result in any adverse impacts on aquatic organisms (including AMR)**

  Environmental protection can be based on blue-green algae (cyanobacteria) or the microbial inhibition concentration (MIC) available from prescribing information. Two different PNECs:

  $PNEC_{ENV}$ = Cyanobacteria (blue-green algae) lowest no effect concentration/10

  $PNEC_{MIC}$: Bengtsson-Palme *et al* 2016 paper listed $PNEC_{MIC}$ for all common antibiotics

- **AMR Alliance has agreed that where there are values for both $PNEC_{ENV}$ and $PNEC_{MIC}$ the lower of the two values will be applied. This will reduce selection pressure for AMR.**

AMR Industry Alliance Discharge Targets

- Revised and updated January 2020:

AMR Alliance Science-Based PNEC Targets for Risk Assessments

Active Pharmaceutical Ingredient	$PNEC_{ENV}$ (µg/L)	$PNEC_{MIC}$ (µg/L)	Lowest Value (µg/L)
Amikacin	N/A	16.00	16.00
Amoxicillin	0.57	0.25	0.25
Amphotericin B	N/A	0.02	0.02
Ampicillin	0.60	0.25	0.25
Anidulafungin	N/A	0.02	0.02
Avilamycin	125.00	8.00	8.00
Azithromycin	0.03	0.25	0.03
Aztreonam	N/A	0.50	0.50
Bacitracin	114.59	8.00	8.00
Bedaquiline	0.08	N/A	0.08
Capreomycin	N/A	2.00	2.00
Cefaclor	N/A	0.50	0.50
Cefadroxil	0.14	2.00	0.14

Wastewater Discharges: PEC

1 Predicted Environmental Concentration **(PEC)** → ***How much API will end up in the environment?***

API Mass Balance Fundamental

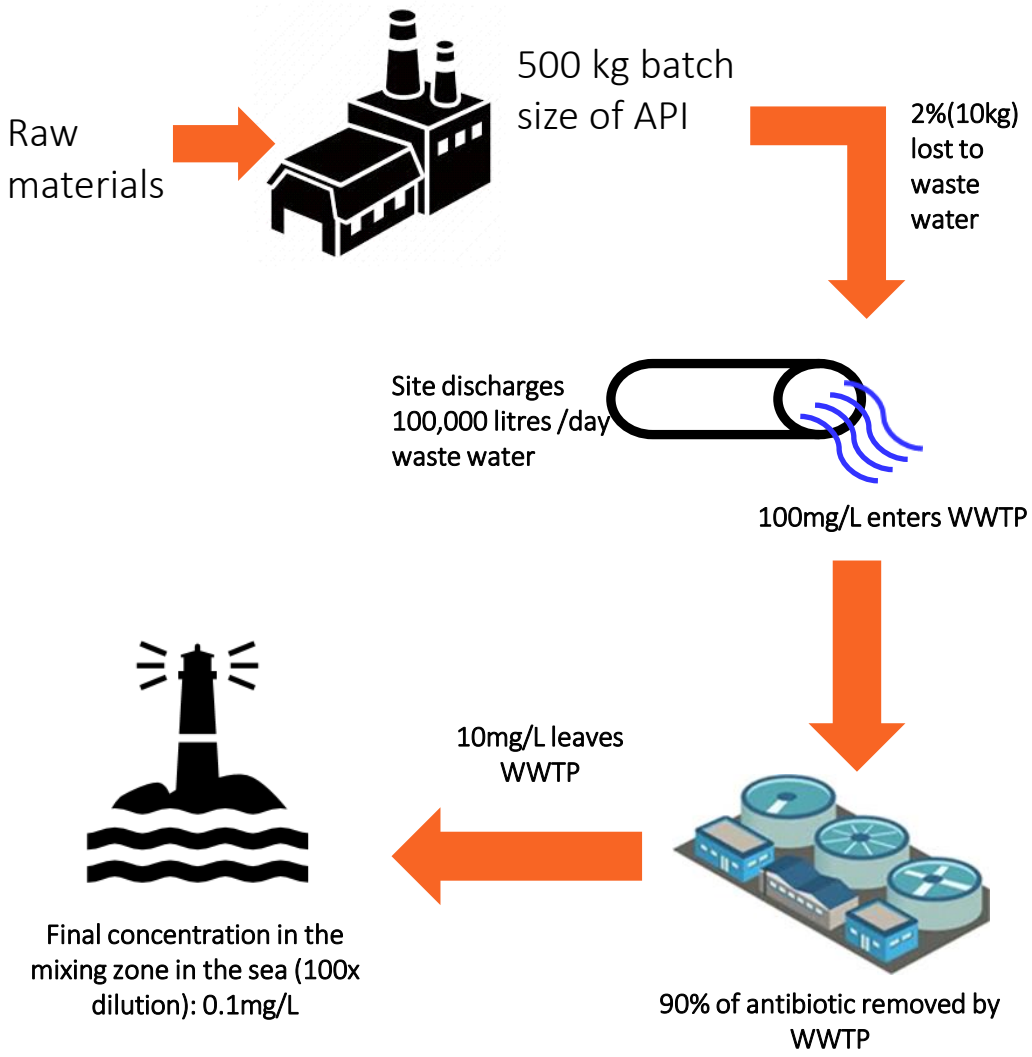
Mass (M) = Flow (Q) x Concentration (C)

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

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

Mass Balance Approach to Site Environmental Risk Assessment

- Estimate/calculate losses of API into waste water during manufacturing process
- Apply average flow rates of waste water & mixing with other effluent streams:
  - From the manufacturing process or site
  - During waste water treatment (on or off site)
- Robust estimates (or actual measured values) for the % removal of API during waste water treatment
- Estimate concentration in final mixing zone in the receiving water body. If unknown apply conservative dilution factors:
  - 10x for rivers/lakes
  - 100x for the sea



Manufacturing Site Antibiotic Emissions

How do we assess Environmental Impact?

- Standard Risk Assessment Technique

  Predicted Environmental Concentration - The PEC is a prediction of actual exposure is normally calculated using a conservative Mass Balance approach. It may be refined to a Measured Environmental Concentration (MEC) using analytical sampling and monitoring data.

PEC/PNEC > 1 means there is a **potential risk** to the environment

PEC/PNEC ≤ 1 means there is a **low/insignificant risk** to the environment

Summary

- PiE and AMR is an area of growing importance and concern. Increase in focus:
  - Scientific literature
  - NGO concerns
  - Media attention
  - Public concern
  - Legislative (e.g. Indian Draft regulations)/ Regulatory interest
- Manufacturing discharges of antibiotics could cause localised AMR hotspots
- AMR Industry Alliance committed to tackling the issue of antibiotic manufacturing discharges
  - Common Antibiotic Manufacturing Framework: best practice guide on managing antibiotic waste
  - Science based wastewater discharge targets (PNECs)
    - Predicted Environmental Concentration (PEC) calculated by mass balance approach

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PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Building responsible supply chains

Managing Antibiotics in the Environment Risk from Manufacture

JONATHAN STANWAY

BIOTECHNOLOGY & ENVIRONMENTAL DOWNSTREAM MANAGER

GLAXOSMITHKLINE

Speaker Bio

Jon Stanway

BEng (Chemical Engineering) MSc (Biochemical Engineering)

CEng Chartered Engineer of the Institute of Chemical Engineering (IChemE)

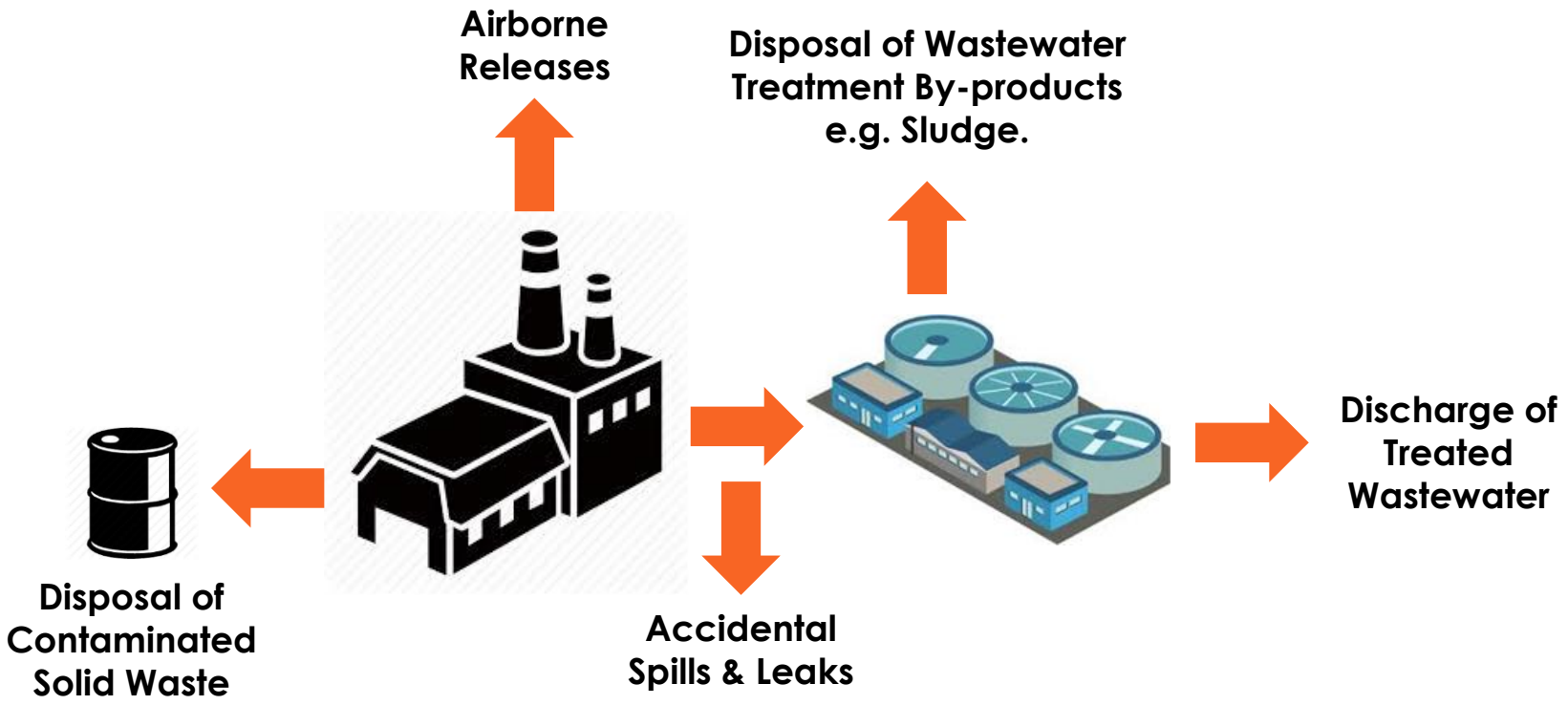
14 years at GSK across API development and manufacture.

BIOTECHNOLOGY & ENVIRONMENTAL DOWNSTREAM MANAGER, GSK

- Pharmaceuticals in the Environment expert
  - Manufacturing controls and wastewater treatment
  - AMR Industry Alliance Manufacturing Roadmap risk assessment & compliance
  - Mass Balance calculation and analytical characterisation.
- Small molecule biotechnology industrialization.

Antibiotics in the Environment Vectors

- Multiple potential sources of antibiotics in the environment from manufacturing operations.
- A robust management system should assess and control the risk from all potential sources.



Antibiotics in the Environment Risk Mitigation

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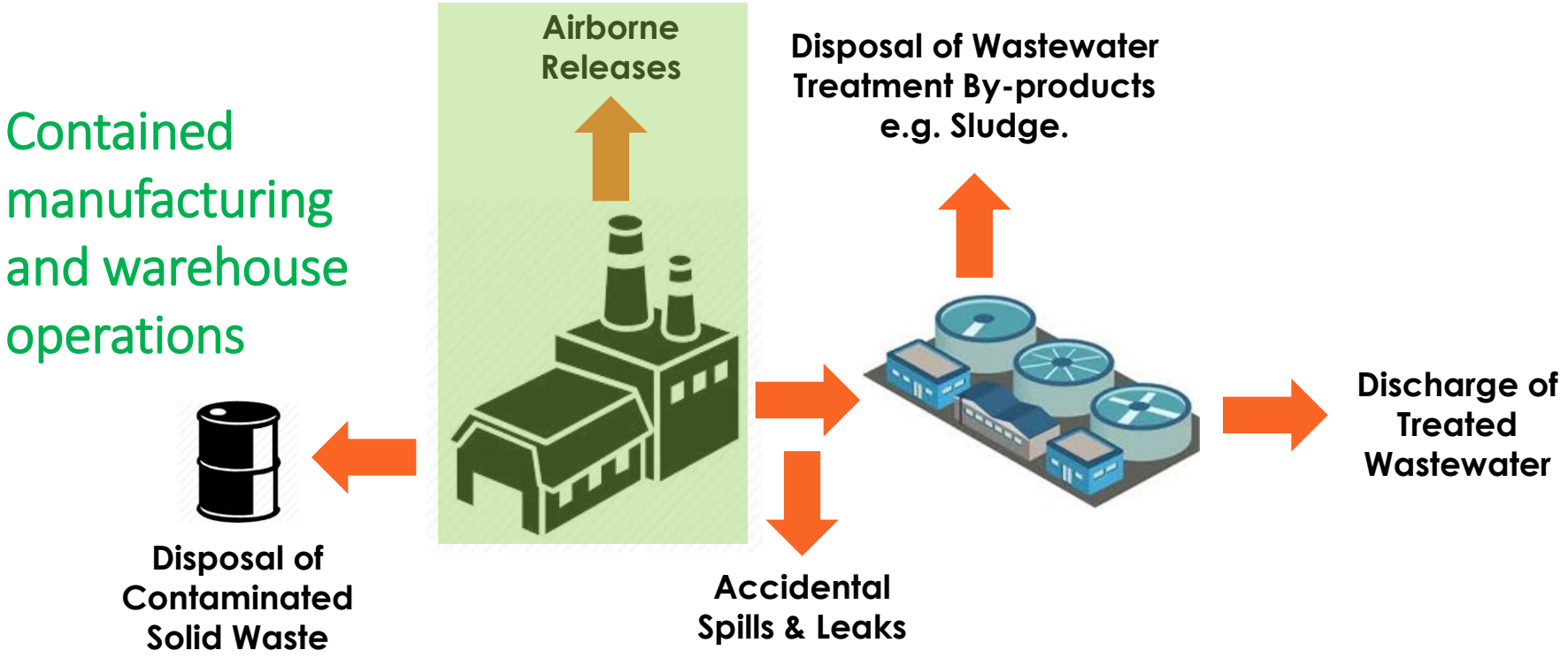

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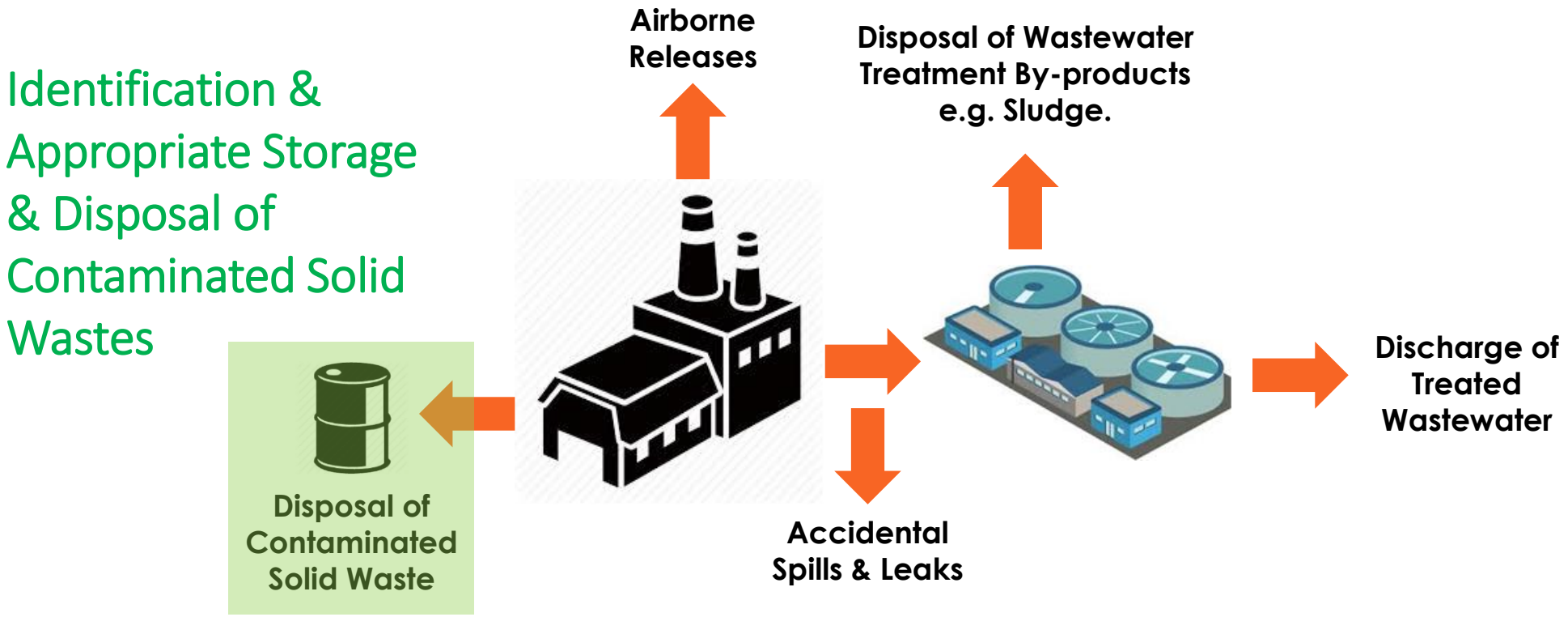

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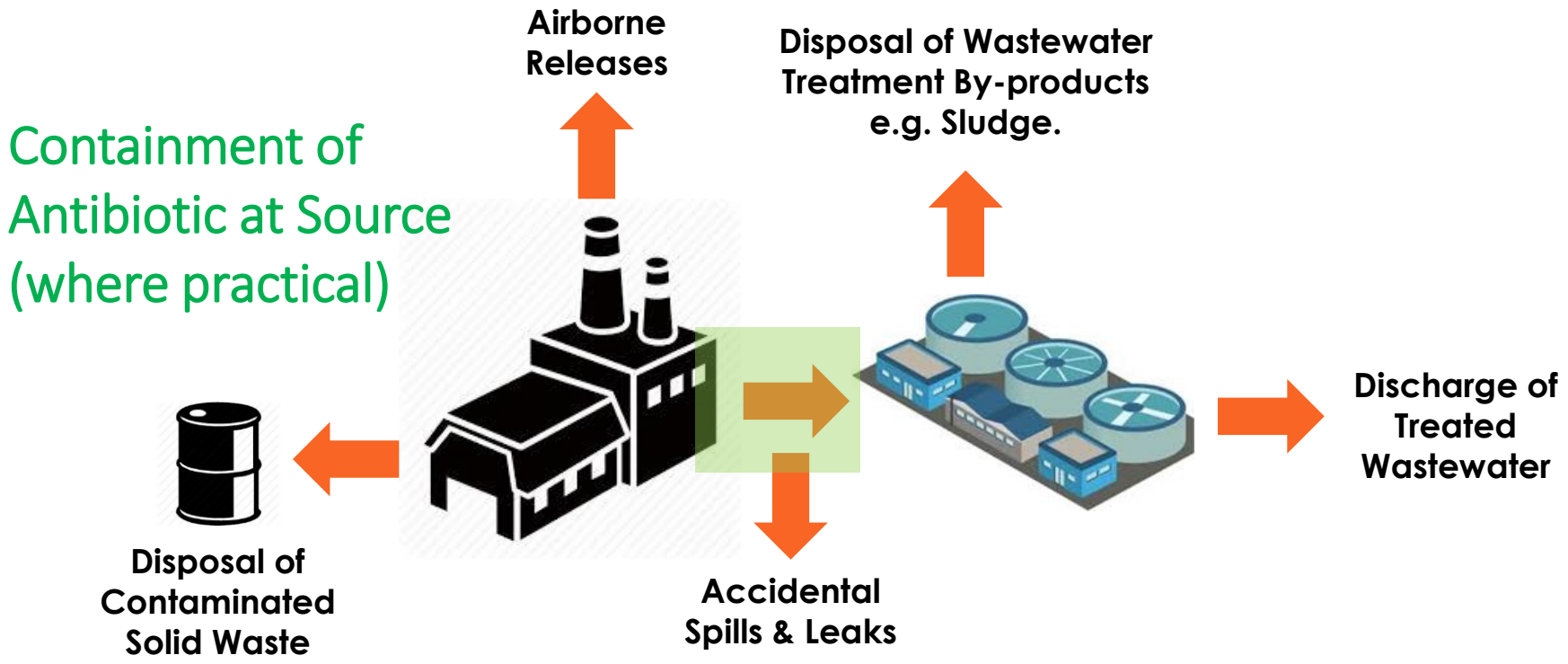

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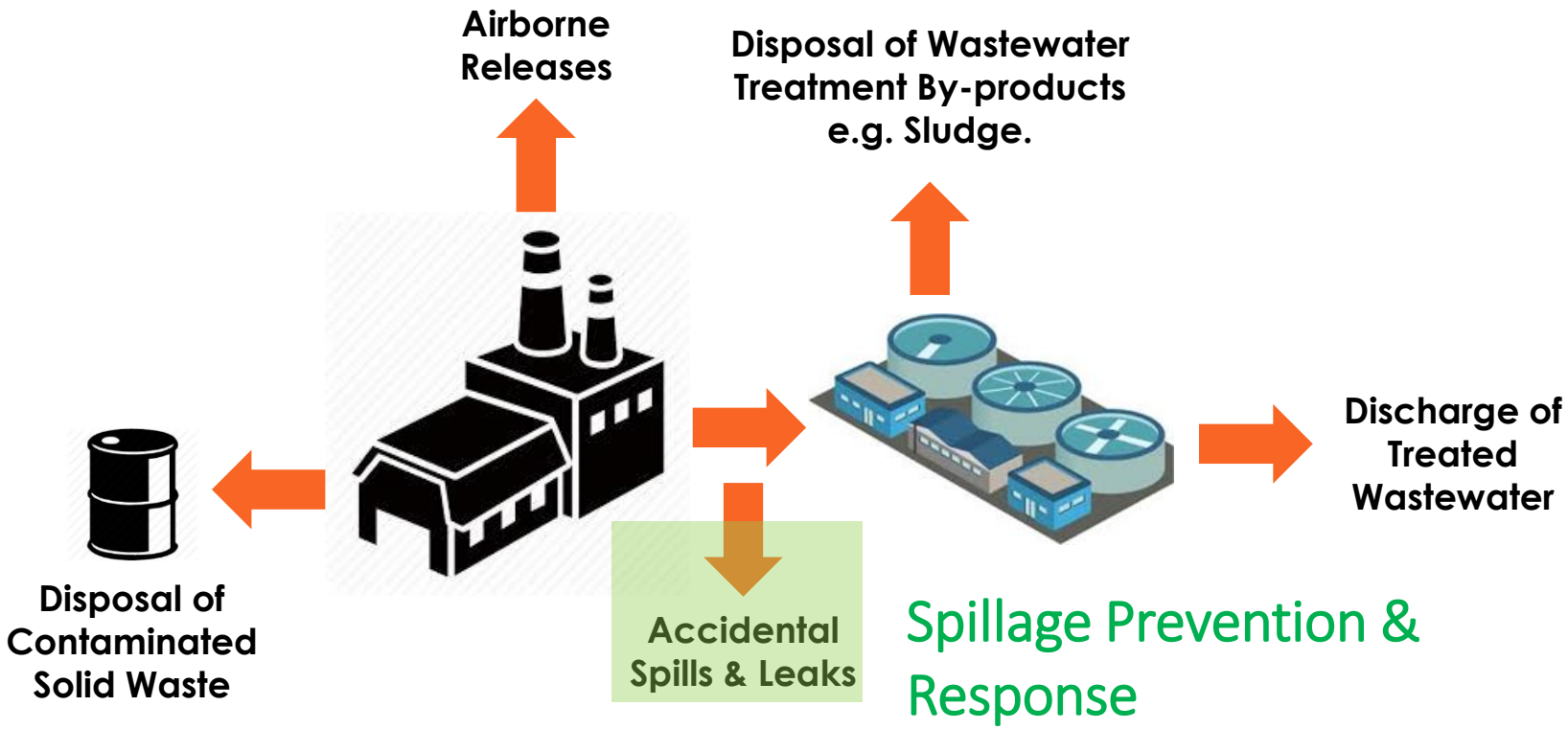

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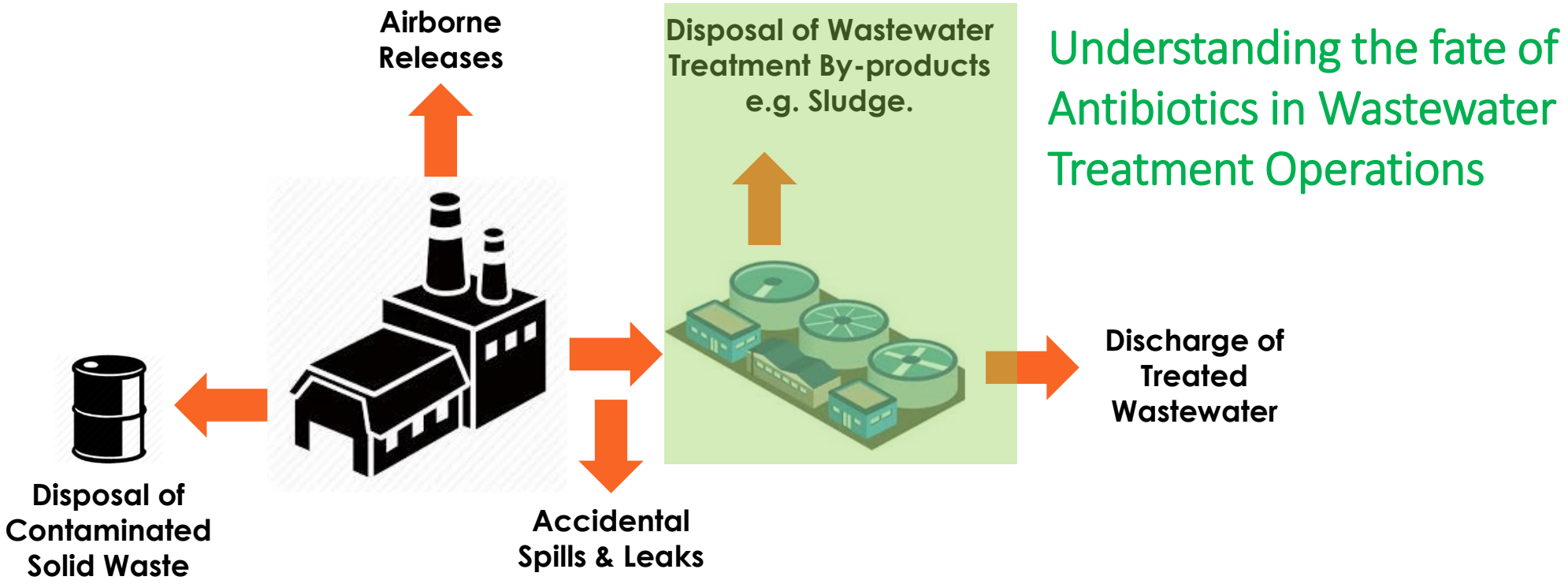

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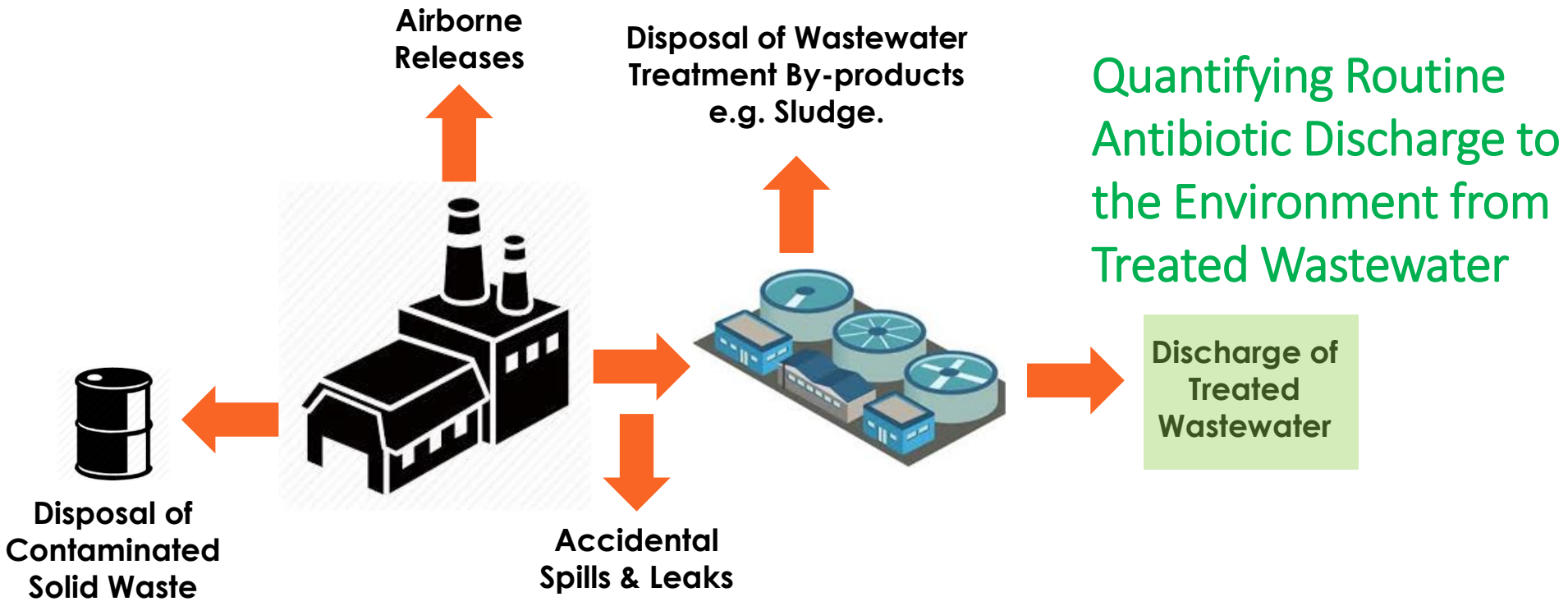

Control within Manufacturing Areas

- Facilities should be designed and operated to prevent fugitive releases to the environment.
  - Processes contained in closed equipment wherever practicable
  - Potential for airborne releases minimised through vent abatement e.g. filters, scrubbers or cyclones.
  - Sealed or segregated from external areas e.g. within enclosed buildings, airlocks, pressure cascades etc.
- Where spillage can occur, this should be mitigated through e.g.;
  - Use of routinely maintained bunds
  - Routing of floor drains to wastewater treatment or plugging of floor drains during high risk activities.
  - Routine cleaning of manufacturing areas and timely clean-up of spills.
- Storage areas should be of sufficient capacity to hold all materials and be sheltered from weather elements.
- Where storm drains are not routed to wastewater treatment, separation of these drains from potential sources of antibiotic contamination should be assured.

Containment of Antibiotic at Source

- Where practicable, contain antibiotic at source to minimise overall and peak load on downstream wastewater treatment.
- Containment at source can be achieved by the following;
  - Process optimisation to minimise process yield losses.
  - Separation of high antibiotic concentration waste within manufacturing areas for disposal by incineration, through
    - Dry/vacuum cleaning.
    - Capture of equipment rinse washes.
    - Solvent recovery.
  - Use of processing or pre-treatment conditions/techniques which inactivate or destroy the antibiotic molecule prior to discharge to wastewater treatment e.g. application of extreme pH or high temperature conditions.
    - e.g. β-lactams are readily degraded at high pH conditions.

Examples: Containment of Antibiotic at Source

- GSK South East Asia site
  - Antibiotic ointment manufacture of 5 different antibiotic APIs
  - Contain antibiotic at source by physically removing product residues from equipment prior to rinsing with recovered solids and first rinses incinerated.
- GSK European site
  - Steriles and ointment manufacture of 5 different antibiotic APIs
  - Airborne losses minimised through use of HEPA filters on process vents. Manufacturing areas are sealed.
  - First cleaning rinses of equipment are collected for incineration. A thermal pre-treatment is employed for 2 antibiotics

Solid Waste Management

- Antibiotic and antibiotic-contaminated solid waste may constitute;
  - Process waste e.g. fermentation bio-sludge, waste and rejected product, laboratory waste.
  - Contaminated packaging, personnel protective equipment (PPE) or consumables.
  - Wastewater treatment wastes (e.g. biosolid, sediments, spent carbon, membranes).
- Solid waste storage/transport/disposal should comply with regulations, permits, licenses and authorisation.
- Where incineration or thermal oxidation (best-practices) are not used, containment, pre-treatment, inertisation and monitoring (e.g. analysis of leachate) controls should be in place to appropriately manage the risk of soil or groundwater contamination from leaching or spills.
- Solid waste containers should be;
  - Compatible, robust and maintained in good condition.
  - Kept closed except when filling/emptying.
  - Stored with appropriate labelling and segregation to ensure appropriate disposal.

Examples: Solid Waste Management

- GSK North American site
  - Liquids, solids and derm products involving 4 antibiotic APIs.
  - Antibiotic solid waste includes recovered material from physical cleaning of production equipment which is collected and contained in solid, leak-tight containers within plant rooms and sent to a third party for incineration.
  - Recovered biosolid and clarified solids from the municipal WWTP are also incinerated.
- GSK Far East site
  - Manufacture of oral solid doses & creams involving 1 antibiotic API
  - Site waste (waste production materials & WWTP biosolid) stored in labelled containers in a dedicated waste storage warehouse, packed & palletized to minimise spill risk with transportation in sealed trucks to incineration.

Wastewater Treatment

- Complete containment at source or recycle/incineration of wastewater possible for some sites.
- Otherwise, effective wastewater treatment by a robust and proven methodology should be in place to control environmental antibiotic discharge to below established discharge limits, even under worst-case discharge scenarios.
- Wastewater treatment processes fall into two categories. See also Caldwell et al. (2016) for an overview of treatment technologies.
    - Separation Techniques: Carbon/resin adsorption, membrane filtration, oil separation and flocculation/coagulation (where solubility is low). Require appropriate disposal of recovered antibiotic.
    - Destruction Techniques: pH/thermal hydrolysis, advanced oxidation processes (e.g. ozonation, UV), chlorination. Requires understanding of degradation product impact.
- Removal mechanism in biological treatment a combination of biodegradation and adsorption to sludge particles. Containment of antibiotic resistant organisms is a further consideration.

Antibiotic Quantification

- Control of antibiotic discharge to within the environmental limits (PNECs) should be established by robust calculation and or monitoring. Calculation by mass balance should include the following parameters;
  - Worst-case losses of antibiotic to wastewater, accounting for any containment at source techniques.
  - Removal efficiency of the antibiotic in the wastewater treatment processes. Ideally be based on analytical characterisation of the specific systems as assumptions based on measured COD removal efficiency are unlikely to be accurate and extrapolation of literature data may not be representative of actual performance.
  - Estimation/measurement of the flowrate at the point of environmental discharge of wastewater. Where this data is unavailable, typical conservative assumed values for dilution of 10x (river) and 100x (sea) are commonly applied, where appropriate.
- Where analytical testing results in “none detected” results, these should be interpreted as results at the limit of detection of the method rather than confirming the absence of antibiotic.

Example: Treatment & Quantification

- European GSK beta-lactam antibiotic manufacturing site.
  - Antibiotic residues contained at source through the recovery of equipment heels prior to equipment cleaning to minimise the quantity discharged.
  - Wastewater undergoes a thermal treatment (manufactured antibiotic is thermally unstable) prior to discharge to marine outfall.
  - Composite samples of wastewater prior to discharge analysed by a sensitive in-house LC-MS/MS method with a low (ppb) limit of detection determined, which confirmed control of the antibiotic to 6% of the PNEC limit.

Zero-Liquid Discharge

- Important to differentiate between True ZLD (full recycle) or **No offsite discharge?**
- Quantification of API in wastewater may not be required where treated wastewater is fully recycled e.g. to utilities without any environmental discharge.
    - Quantification may still be beneficial to inform antibiotic in the environment risk assessment of e.g. WWTP biosolid.
- For sites discharging treated wastewater for onsite irrigation, understanding API discharge concentration is of particular importance;
    - No dilution/buffering effect from downstream flow.
    - Potential accumulation effects in soil.
- Common approach to apply surface water PNEC limits for soil discharge where soil specific PNEC limits are not available.

Permit Compliance

- A valid authorization, license or permit should be in place with compliance demonstrated and reported for all requirements/parameters e.g. related to;
  - Water intake and discharge quantity and quantity.
  - Disposal routes/volume of solid waste etc.
  - Type and quantity of antibiotics manufactured on site.
- In the event of the site being out of consent or receiving any formal complaints, warning letters, enforcement notices, court proceedings, prosecutions or fines in relation to effluent discharge incidents, an investigation should be carried out and robust remedial, corrective or preventative actions taken in response.
- Where site or regulatory changes could result in a failure to meet regulatory wastewater limits, a plan should be in place to mitigate the risks.

Risk Assessment and Mitigation

- Site risk assessments should consider the potential for environmental contamination by antibiotics via all potential vectors whether intended and routine or unintended and fugitive.
  - **Land** – e.g. potential for soil contamination.
  - **Water** – e.g. potential for surface and groundwater contamination.
  - **Air**
- Risk assessments should include potential for impact from foreseeable external environmental factors (e.g. heavy rains and flooding).
- Mitigating controls should be identified and in place, proportional to the severity of the consequences and likelihood of occurrence. These can be a combination of;
  - Preventative controls e.g. engineering design.
  - Responsive controls e.g. emergency response processes.
- Where procedural controls form part of the risk mitigation strategy these should be documented in up to date standard operating procedures, with relevant personnel trained.

Maintenance

- Wastewater monitoring, treatment and transfer equipment and pipelines should be fit for purpose and robust by design with preventative maintenance programmes in place based on criticality, manufacturer's recommendations and historic failure rates.
- Maintenance programmes should include the periodic integrity inspection of vessels, bunds and pipework, including underground pipework by (as appropriate);
    - Visual inspection
    - Camera inspection
    - Use of tracer chemicals
    - Hydraulic/pressure leak testing.

Examples: Maintenance

- GSK Far East site
  - Local manufacture site involving 1 antibiotic API
  - Integrity inspection performed 3-yearly (annual inspection on rolling rota) by camera
- GSK Far East site
  - Manufacture site involving 1 antibiotic API
  - Underground drainage routinely inspected on 2-yearly basis
  - RBI integrity test through CCTV visual and mechanical inspection

Spillage Response

- There should be a proceduralised response to near misses, leaks and spills on site, which all relevant personnel are trained in, to ensure a rapid and effective response to minimise environmental impact. Training may be supported by routine drills, particularly if there is a high-severity risk associated with potential incidents.
- Processes should also cover;
    - Timely reporting of events to the business and relevant authorities.
    - Determining the root cause of the issue so that robust remedial, corrective and preventative actions are implemented to prevent recurrence.

Example: Spillage Response

- GSK Far East site
  - Manufacture of oral solid doses & creams involving 1 antibiotic API
  - Site has an Emergency Response Plan
  - Defines the appropriate notification of authorities
  - Annual drill to practice the response
  - Procedures in place to appropriately handle spills and leaks and WWTP personnel are trained in spillage response
  - In the event of emergency conditions manufacturing operations and the WWTP is shut down.

Wastewater Characterisation

- All sources of wastewater from site operations should be characterized and evaluated for treatability through the maintenance of an up to date, and routinely reviewed, water balance.
    - Based, wherever practicable on measured flow rates in the feed and final discharge from the site and ideally also from individual production areas and wastewater treatment plants.
    - Flow meters should be routinely calibrated.
- Where there are unaccounted volumes in the water balance an investigation should be conducted and corrective actions identified to address these, e.g. through the installation of additional flow monitoring points.

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Exam (20 mins) & Feedback survey

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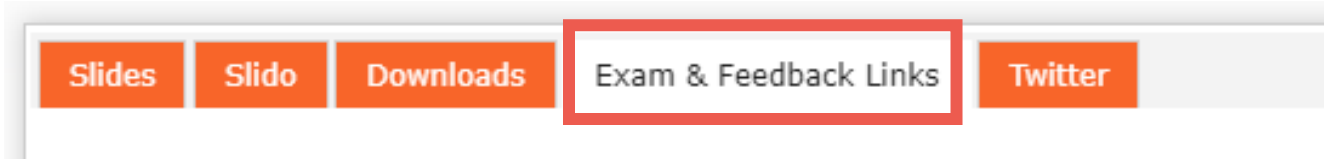

Exam QR Code

Feedback survey QR Code

We recommend everyone to take the exam. Only auditors joining all the sessions and exams will receive certificates of participation.

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