COMMON ANTIBIOTIC MANUFACTURING FRAMEWORK

The Antimicrobial Resistance (AMR) Roadmap Companies recognize and understand concerns raised by stakeholders regarding the presence of pharmaceuticals in the environment (PIE). The major source of pharmaceuticals entering into the environment is via patient excretion following use of medicine that is taken to prevent, cure or alleviate a medical condition. A comparatively smaller contribution to PIE stems from emissions from industry during manufacture of the pharmaceuticals.[1]

While the overall contribution of pharmaceutical manufacturing to PIE is relatively low, there is the potential for localized impacts to be created in cases where manufacturing emissions are inadequately managed. Ensuring the use of appropriate environmental risk management measures to adequately control manufacturing effluent emissions remains an important area of focus for the pharmaceutical industry and is an approach already in place in a number of companies.[2] We are aligned in our intent and are ready to build and share common practices.

Reports of active pharmaceutical ingredients (APIs) in water from pharmaceutical manufacturing indicate concentrations have reached potentially harmful levels when wastewater discharges are not sufficiently controlled at some facilities,[3] highlighting the importance of effective control of API emissions from manufacturing, both in production of the API itself and its formulation into drug products for patient use.

Environmental regulations pertaining to wastewater discharges from manufacturing, already generally apply to pharmaceutical production. However, many socially and environmentally responsible companies go beyond compliance with the basic regulatory requirements for chemical manufacturers (e.g., control of pH, biological oxygen demand, chemical oxygen demand)[4] and establish environmental protection goals to evaluate and reduce potential environmental risk from production of their products.

Currently, most programs focus on potential toxicity to aquatic species, upsets to wastewater treatment plants or potential toxicity in human drinking water. Emission limits, specifically for preventing antimicrobial resistance, are currently under development. The AMR Roadmap signatories are committed to achieving this goal and are reliant on the evolving science as a means to arriving at a consistent methodology for these limits by 2020.

The Antibiotic Manufacturing Framework provides a methodology and set of minimum requirements needed to conduct a site risk evaluation of both macro and micro controls in our supply chains. Company expectations, including this Framework, will be communicated within the AMR Roadmap signatory companies and their supply chains.

[1] Aga DS .2008. Advances in the Analysis of Pharmaceuticals in the Aquatic Environment. In Aga DS, ed, Fate of Pharmaceuticals in the Environment and in Water Treatment Systems. CRC Press, Taylor & Francis Group, Boca Raton Fl

[2] Caldwell et at Environmental Toxicology & Chemistry Vo 5, No.4 pp813-822, 2016 http://onlinelibrary.wiley.com/doi/10.1002/etc.3163/pdf

[3] Larsson et al Effluent from drug manufactures contains extremely high levels of pharmaceuticals, Journal of Hazardous Materials Volume 148, Issue 3, 30 September 2007, Pages 751-755 http://www.sciencedirect.com/science/article/pii/S0304389407009909?via%3Dihub

[4] Tell et al, Limiting APIs in Manufacturing Effluent, Contract Pharma, 02.06.16 http://www.contractpharma.com/issues/2016-06-01/view_features/limiting-apis-in-manufacturing-effluent/

ANTIBIOTIC MANUFACTURING FRAMEWORK

MINIMUM EXPECTATIONS:

- Compliance with:
  - Local laws and regulations
  - Environmental permits
  - Company standards, Codes of conduct
  - Pharmaceutical Supply Chain Initiative's (PSCI) Pharmaceutical Industry Principles
  - No untreated discharge of manufacturing waste containing antibiotic
- Robust EHS programs, evaluated periodically for efficacy
- Appropriate training is completed in line with industry best practice
- Exercise appropriate duty of care for all discharges and waste streams containing antibiotics
- Allow / facilitate audits as requested, develop and execute plans to address audit findings
- Follow-up conducted for assessments and audits conducted

Note: Audit reports will remain confidential between the company and the supplier or manufacturing site subject to the audit. Audit reports can be shared on the PSCI data base with those member companies that have been granted permission from the supplier. (PSCI shares audit reports among member companies with the supplier's agreement). Companies may opt to publicly report aggregate audit information as part of their overall EHS program reporting.

MINIMUM REQUIREMENTS FOR ENVIRONMENTAL PROGRAMS:

The Framework elements below focus on environmental compliance and appropriate antibiotic discharge management, in addition to expected air emissions control, safety, and health programs.

Water Management Program

Principle: Compliance with all applicable regulations. All required environmental permits, licenses, information registrations and restrictions are in place, available for review, and their operational and reporting requirements are followed. Systems are in place for the management of water discharges. Any wastewater or wastewater sludge from on-site wastewater treatment operations with the potential to adversely impact human or environmental health is managed, controlled, and treated prior to release to the environment. Systems are in place to prevent and mitigate accidental spills and releases to the environment.

1) Site possesses a valid authorization/license/permit for water intake (i.e. from groundwater, river or public system) and discharge. Compliance with each condition in the authorization/ license/ permit is demonstrated.
2) Levels of antibiotic in process wastewater are quantified e.g. mass balance.
3) Wastewater sources from operations are characterized and evaluated for treatability and control.
4) Effective wastewater treatment is provided (e.g., neutralization, clarification, settling, inactivation, biological or chemical treatment).
5) Water/wastewater monitoring devices and treatment systems are in good operating condition and appropriately maintained (e.g. in accordance with manufacturer's recommendations).

6) Biomass from fermentation is managed in compliance with all local regulations.

7) Sludge from process wastewater treatment is managed in compliance with all local regulations.

8) Assessments are conducted to determine potential risk from sludge application to land.

9) Samples are collected, stored, and analyzed with results reported in accordance with local regulatory requirements.

10) Drinking water is treated to be safe for human consumption and meet local regulatory standards or WHO drinking water guidelines in absence of local standards. Water systems that could be impacted by contamination are tested for compounds of concern.

11) Process areas (e.g., tanks, container storage areas, and process sewer systems) are designed, constructed and operated to prevent spills or releases to the environment.

12) Systems are in place to prevent soil, surface water, or groundwater contamination.

Solid Waste Management Program

Principles: Compliance with all applicable regulations. All required environmental permits, licenses, information registrations and restrictions are obtained and available for review, and their operational and reporting requirements are followed. Systems are in place for the safe handling, movement, storage, recycling, reuse, and disposal of waste. Waste with the potential to adversely impact human health or the environment is managed, controlled and treated prior to release to the environment. Systems are in place to prevent and mitigate accidental spills and releases to the environment. Any unpermitted release is reported to the proper authorities and remedial measures are instituted to prevent reoccurrence and address impacts associated with said release. Solid waste management is important to demonstrate control and to prevent an unintended subsequent release.

1) Waste classification, labeling, storage and disposal methods are in accordance with the hazard characteristics of the waste, and in accordance with regulatory requirements, including:

    a) Waste containers are labeled with contents, hazard characteristics (e.g., flammable, biological), and closed once waste is placed in the container.

    b) Disposal methods are based on waste characteristics. Records (e.g., waste classification determinations including analytical results, letters from waste contractors, and certificates of destruction) are maintained.

    Waste disposal contractors possess authorizations/certifications from regulatory authorities to manage specific waste streams in accordance with local regulations.

2) Waste is stored in a manner to prevent discharges and unsafe conditions, such as:

    a. Material is stored in quantities not exceeding the capacity of spill containment and is sheltered from weather/elements.

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

    c. Incompatible wastes and their spill containment are properly segregated (e.g. acids and bases)

    d. Solid wastes are stored in a manner to prevent discharge as the result of rain/storm water run-off.

    e. Biomass from fermentation is managed in compliance with all local regulations to prevent environmental pollution.

f. Waste containers are in good condition and compatible with the materials being stored (e.g., free from corrosion, dents, bulges or other impairment that would impact adequate containment) and are maintained closed except during filling and emptying operations.

g. Materials are stored in a manner to prevent events resulting from undesired reactions, incompatibilities, decomposition and/or self-ignition.

3) Fire risks are assessed in the waste storage area. Suitable fire management and suppression measures are applied (e.g., smoke detectors, fire extinguishers, separation walls, fire water retention) .Waste storage areas are segregated and with access limited to authorized personnel.

4) Any landfills or permanent disposal areas for wastes are specifically authorized by regulatory authorities. Containment and monitoring programs are in place.

    a) Programs are in place to manage soil or groundwater contamination from spills.

AUDITS OF ANTIBIOTIC MANUFACTURERS

To ensure that internal and external antibiotics manufacturing facilities (including active pharmaceutical ingredient and formulation) within the supply chain minimize their environmental impact, on-site EHS audits will be performed. The below description concentrates on environmental compliance and antibiotic discharge minimization, but in addition specifies that appropriate air, safety and health assessments will be part of the audits as well. Assessments and audits should be performed by qualified and competent auditors.

Facility Audits

1) Audit antibiotic suppliers at least once every 5 years

    a) Audits may be performed more frequently based on result of previous audits or discovery of heightened risk at the facility

2) Audit scope:

    a) Facility tour

    b) Regulatory compliance assessment (local laws and regulations)

    c) Operating permit compliance verification

    d) Auditing against a defined protocol or management system (e.g., company's supplier standards, PSCI Auditing guidance).

    e) Focus is on areas for Environmental Management, including:

        i) Water management

        ii) Solid Waste management

        iii) Spill prevention and response , chemical storage and handling

        iv) Employee training

3) Audits include:

    a) Records review

        i) Compliance with regulatory requirements and permit conditions

ii) Facility's environmental risk assessment of antibiotic discharges (quantified by mass balance or measurement) and assessed against applicable risk-based targets for discharge concentrations or overall load.

iii) Maintenance plans (for critical equipment and environmental controls)

iv) Incident investigation logs (corrective and preventative actions plans (CAPA)) for relevant incidents)

v) Supplier practices for evaluating their own supply chain

vi) Waste and Wastewater disposal records

b) Facility tour – to assess operating conditions, ensure practices are in place and are being followed as required (not a remote site or paper review)

i) Storm water collection and retention practices and/or systems

ii) On-site Waste Water Treatment Plant(s) (WWTP)

iii) Waste storage

iv) Process and domestic wastewater collection and treatment

v) Extraction or deep wells

vi) Underground and aboveground storage tanks with associated visible piping

vii) Fuel storage locations

viii) Solvent storage and recovery

ix) Warehouses, other physical storage sheds/locations

x) External tours of the entire facility (including discharge locations, pollution control devices, and receiving stream identification and observation)

xi) Fire water retention

4) Audit report:

a) Identify any non-compliance with local laws and regulations

b) Highlight any gaps, deficiencies, or deviations from generally accepted industry practices and/or contractual commitments and communicated expectations related to antibiotics discharges

Note: Audit reports will remain confidential between the company and the supplier or manufacturing site subject to the audit. Audit reports can be shared on the PSCI data base with those member companies that have been granted permission from the supplier. (PSCI shares audit reports among member companies with the supplier's agreement). Companies may opt to publicly report aggregate audit information as part of their overall EHS program reporting

5) Audit follow up:

a) Work with supplier (facility) to develop acceptable action plans for findings

b) Monitor supplier's performance to confirm progress of actions including subsequent remedial action closure consistent with specified timelines

6) Supplier Oversight

a) Monitor results and determine ongoing appropriateness of suppliers

INFORMATION SHARING – BEST PRACTICES

PSCI Webinars on Managing APIs in Manufacturing Effluent:

Webinar recording - managing APIs in manufacturing effluent - 27th Jan 2016

Step-by-step guidance covering the following topics:

- Why is managing active pharmaceutical ingredients (API) in manufacturing effluent important?
- What is the industry doing to improve public perceptions?
- Understanding where you stand at the moment through the maturity ladder concept.
- Establishing and calculating API discharge concentration called the Predicted-No-Effect-Concentration (PNEC).
- Simple steps to reducing API process losses to waste water and what to do when the PNEC is exceeded.
- How to advance your program to the next level.

Webinar recording - managing APIs in manufacturing effluent Part 2 - 15th June 2016

Step-by-step guidance covering the following topics:

- Estimating API losses from the manufacturing process (PEC)
- Establishing the acceptable discharge concentration (PNEC)
- Making low capital investment housekeeping steps to reduce the loss of APIs

Webinar slide deck - managing APIs in manufacturing effluent Part 3 - 25th October 2016

This webinar looked at advanced technologies to reduce API loss with guest speakers from the Temple University WET Centre and AECOM.

Additional Published Resources:

1. Aga DS. 2008. Advances in the Analysis of Pharmaceuticals in the Aquatic Environment. In Aga DS, ed, Fate of Pharmaceuticals in the Environment and in Water Treatment Systems. CRC Press, Taylor & Francis Group, Boca Raton, FL.
2. Caldwell et al, Environmental Toxicology & Chemistry Vo 35, No.4 pp813-822, 2016 http://onlinelibrary.wiley.com/doi/10.1002/etc.3163/pdf "A Risk Based Approach to Manage Active Pharmaceutical Ingredients in Manufacturing Effluent" (This resource may be used to identify practices for assessing potential environmental risks from APIs in manufacturing effluent and outline measures that can be used to reduce the risk, including selective application of available treatment technologies.)
3. Larsson et al Effluent from drug manufactures contains extremely high levels of pharmaceuticals, Journal of Hazardous Materials Volume 148, Issue 3, 30 September 2007, Pages 751-755 http://www.sciencedirect.com/science/article/pii/S0304389407009909?via%3Dihub
4. Tell et al, Limiting APIs in Manufacturing Effluent, Contract Pharma, 02.06.16 http://www.contractpharma.com/issues/2016-06-01/view_features/limiting-apis-in-manufacturing-effluent/
5. Vestel J, Caldwell DJ, Constantine L, D'Aco, VJ, Davidson, T, Dolan, DG, Millard SP, Murray-Smith R, Parke NJ, Ryan JJ, Straub JO, Wilson, P. 2015. Use of Acute and Chronic Ecotoxicity Data in Environmental Risk Assessment of Pharmaceuticals. Environmental Toxicology & Chemistry DOI: 10.1002/etc.3260
6. Sargent EV, Faria E, Pfister T, Sussman RG. 2013. Guidance on the establishment of acceptable daily exposure limits (ADE) to support Risk-Based Manufacture of Pharmaceutical Products. Regulatory Toxicology and Pharmacology 65:242-250.
7. Cunningham V, Olson SBM. 2009. Human health risk assessment from the presence of human pharmaceuticals in the aquatic environment. Regul Toxicol Pharmacol 53:39-45.
8. EU EMA. 2006. Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. In Agency EM, ed, EMEA/CHMP/SWP/4447/00. Committee for Medicinal Products for Human Use (CHMP), London, UK.
9. ECHA. 2008. Guidance on information requirements and chemical safety asssesment. Chapter R.10: Characterisation of dose [concentration]-response for environment. REACH Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006. European Chemicals Agency, Helsinki, Finland.
10. Caldwell DJ, Mastrocco F, Hutchinson TH, Länge R, Heijerick D, Janssen C, Anderson PD, Sumpter JP. 2008. Derivation of an Aquatic Predicted No-Effect Concentration for the Synthetic Hormone, 17α-Ethinyl Estradiol. Environmental Science & Technology 42:7046-7054.
11. Dolan DG, Naumann BD, Sargent EV, Maier A, Dourson ML. 2005. Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations. Regul Toxicol Pharmacol:1-9.
12. Schwab B, Hayes E, Fiori J, Mastrocco F, Roden N, Cragin D, Meyerhoff R, D'Aco V, Anderson P. 2005. Human pharmaceuticals in US surface waters: a human health risk assessment. Regul Toxicol Pharmacol 42:296-312.
13. EPA. 2004. Estimated Per Capita Water Ingestion and Body Weight in the United States–An Update, Washington, DC.
14. Anderson PD, D'Aco VJ, Shanahan P, Chapra SC, Buzby ME, Cunningham VL, DuPlessie BM, Hayes EP, Mastrocco FJ, Parke NJ, Rader JC, Samuelian JH, Schwab BW. 2004. Screening Analysis of Human Pharmaceutical Compounds in U.S. Surface Waters. Environmental Science & Technology 38:838-849.
15. US FDA. 1998. Environmental Assessment of Human Drugs and Biologics Application. In US Food and Drug Administration CfDEaRC, ed.

16. World Health Organization 2015, Global Action Plan on Antimicrobial Resistance, ISBN 978 92 4 150976 3

Example Company Programs Published in the Literature:

Managing Emissions of API from Manufacturing - An Environmental Quality Standard Approach Integrated Environmental Assessment and Management — Volume 8, Number 2—pp. 320–330

2011, SETAC.

Limiting APIs in Manufacturing Effluent – Contract Pharma. Tell et al, 06.02.16.

IPPC Reference on Best Available Techniques for the Manufacture of Organic Fine Chemicals, Chapter 5

This document contains the results of an exchange of information between EU Member States and industries concerning best available technique (BAT) and associated monitoring for the Manufacture of Organic Fine Chemicals.

References to Perform Audits

1) Pharmaceutical Industry Principles for Responsible Supply Chain Management (PSCI) - *Guidance for Implementing The Principles* https://pscinitiative.org/resource?resource=2
2) PSCI Audit Programme Guidance
    a. This document is designed to be used by PSCI members, audit contractors and suppliers. It provides a detailed overview of the audit process and corresponding roles and responsibilities at each stage of the process.
3) PSCI Pre-Audit Document Request List
4) Full PSCI SAQ & Audit Report Template for Core Suppliers, External Manufacturers, Component and Material Suppliers
    a. PSCI Self-Assessment Questionnaire and Audit Report Template for Core Suppliers, External Manufacturers, Component and Material Suppliers (Version 4, October 2016)
    b. General information, Facility Background: Pages 1 – 5
    c. Management Systems: Pages 6 – 8
    d. Ethics: Pages 9 – 10
    e. Labor: Pages 11 – 14
    f. Environmental Protection: Pages 15 – 20
    g. Health & Safety Compliance and Risk Management: Pages 21 – 32
    h. Biological Safety: Pages 32 – 33