[PUBLICATION]

Responsible Antibiotics Manufacturing Platform (RAMP) Framework

A toolbox of options for responsible manufacturing to reduce the risks of antimicrobial resistance.

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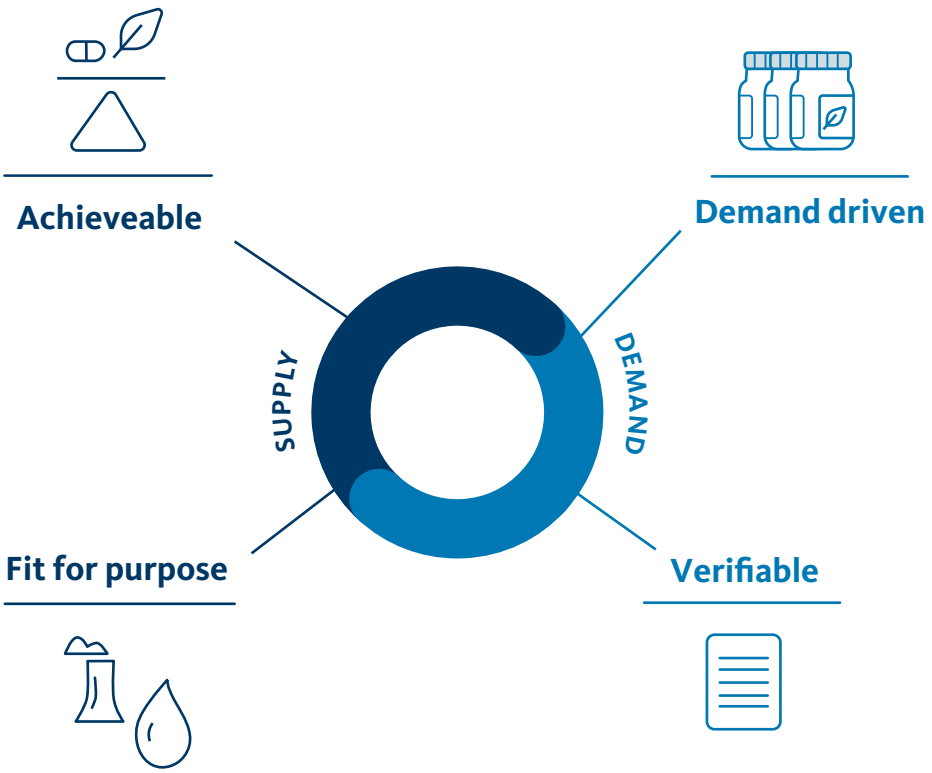
RAMP Framework

For responsible antibiotic manufacturing

Antibiotics entering the environment through manufacturing waste streams can contribute to the risk of promoting antibiotic resistance. Industry, procurers, and other stakeholders have attempted to address this risk through disparate approaches. However, harmonizaton of criteria is crucial to provide incentives and a level playing field for scaled implementation of improved industry practice. The RAMP Framework has identified the following four factors that should define criteria of responsible antibiotics manufacturing:



Achieveable

Benchmarking commercially available technical solutions against the framework

Fit for purpose

Prevention of selective concentrations of antibiotics, which is defined as meeting scientifically derived concentration limits at the point of emission

Demand driven

Connecting the supply and demand side, while being applicable in various stakeholder contexts (procurement, regulation, GMP, investors, scientific community) to promote policy change

Verifiable

Direct water sampling or using proxies such as mass balance calculations or water quality measurements of established parameters that can be correlated to API concentrations

Use of industry accepted best available technologies that ensure meeting the objective

Summary

Antibiotic pollution from manufacturing is an unnecessary and avoidable driver of antimicrobial resistance (AMR) that is not yet sufficiently addressed. Usage of antibiotics and improper waste management and disposal serve for the bulk of antibiotics entering the environment in terms of global flows and volumes. Nevertheless, manufacturing emissions have the highest likelihood of generating locally high, i.e., selective concentrations. The lack of agreed systematic monitoring across either public or industry sectors makes it close to impossible to attribute environmental concentrations to individual points of emission. This, in turn, makes it difficult for progressive market players, be it on the supply or demand side of the market, to define the right criteria for incentivizing responsible manufacturing.

Therefore, the core objective of what responsible manufacturing means with respect to mitigating AMR risks needs to be as clear as possible:

To prevent exposure of bacteria to selective concentrations of antibiotics.

Voluntary initiatives like the standard by the AMR Industry Alliance and the corresponding certification by the British Standards Institute are important first steps in this direction, and the pharmaceutical industry should be acknowledged for taking the lead on setting international standards in responsible antibiotic manufacturing. However, challenges remain in relation to science and methodology. This has led to a situation where parts of the pharmaceutical industry are introducing manufacturing standards ahead of universal agreement among companies, regulators, governments, scientists, environmentalists, and international organisations on what constitutes the best standards for antibiotic manufacturing. The result is insufficient cooperation among stakeholders, lack of coherence in addressing antibiotic pollution and, a risk of locking-in standards that do not sufficiently meet the needs of other stakeholders and the community, or adequately address environmental issues in the long-term.

Universal quality requirements for any meaningful standard in this context should be the following:

1. Scientifically fit for purpose
2. Technically achievable
3. Verifiable
4. Demand driven.

The weak points with the AMRIA standard are that:

- The proposed methodology systematically allows for exposure of bacteria to selective concentrations by applying target concentrations after dilution in the recipient waterbody. Depending on the waterbody, it can take significant space and time to achieve this dilution.
- Verification in the suggested industry standard is largely based on modelled waste volumes. While this type of proxy is essential, given the difficulty of direct sampling, calibration against actual environmental concentrations must be part of the approach. By applying target concentrations in the recipient water body, the industry standard makes it impossible to attribute measured environmental concentrations to individual points of emission. This leaves the possibility of confusion over the contribution of other sources of pollution like hospitals or agriculture instead of providing transparent information about industry emissions.

Beyond this critical gap, the voluntary industry standard correctly points towards the need for adequate environmental management practice, including liquid and solid waste management. The main reason for this is that any approach based on direct concentration measurements has strong limitations:

1. The batch-based character of the production makes it easy to "miss the peak" unless integrated samples are taken over time and the variable volume of effluents makes it challenging to interpret emission levels.
2. Sampling and lab-analysis is costly, and it is an ex-post assessment not allowing for immediate response. However, real time sensors or other types of automated monitoring are currently not available.

This current lack of appropriate environmental data or monitoring and cost-effective technologies leads to the need for proxies that can serve as proof of compliance by:

1. Modelling the expected concentrations (based on mass balance) for the point of emission,
2. Defining the required types of interventions (e.g., treatment technologies) or
3. Defining required management practice.

The **Responsible Antibiotics Manufacturing Platform (RAMP)** is a collaboration platform hosted by Stockholm International Water Institute (SIWI), together with Shawview Consulting and Spans Envirotech, funded by the Swiss Agency for Development and Cooperation (SDC). RAMP brings together supply and demand side perspective of antibiotic manufacturing. Demand is seen as any kind of policy or market instrument that can impose sustainability criteria on manufacturers, including public procurement, healthcare policies, environmental and pharmaceutical regulation.

RAMP has developed an independent framework by systematizing the different options and levels for compliance control and suggesting criteria that are applicable

as an interface between the demand side and the supplier. Focusing on criteria that are in the immediate control of the manufacturer or subcontractor (e.g., waste(water) treatment facilities), the RAMP Framework aims to be universally applicable and contribute to transparency and accountability between the relevant parties. The key objective is to help drive consensus and collaboration on the best practice antibiotic manufacturing standards among all stakeholders as a precondition to mitigating AMR risks from manufacturing.

Recommendations

Being a time-limited project, RAMP engages with potential technical solution providers to ensure technical achievability and verifiability based on the available science for target values and the specific technologies. But to achieve the desired impact of mitigating AMR risks from manufacturing by preventing selective concentrations of antibiotics in manufacturing waste streams, a higher degree of collaboration, coherence and governance is needed. This requires industry implementation and regulation or incentives to be based on improved science-based targets, technologies, and monitoring. To achieve this, RAMP recommends:

- **An independent scientific panel** that defines, reviews and updates target concentrations based on available science, and promotes cooperation to improve scientific evidence around antibiotic pollution, its causes, effects, and remediation.
- **Specifications of technology requirements** comparable to Best Available Technology (BAT) reference documents (BREF) through the same scientific panel or e.g., OECD.
- **A global multi stakeholder partnership to support coherent application** of sustainability criteria in relevant policy and market instruments to guide and support industry practice.
- **Increased laboratory and monitoring capacity and new technologies** (e.g., real time sensors) to improve and simplify compliance control.

A Centre of Excellence for capacity building and improved access to knowledge and technologies, technical piloting, and testbeds.

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1. Foreword/Context

What is RAMP?

The Responsible Antibiotics Manufacturing Platform (RAMP) is a collaboration platform hosted by Stockholm International Water Institute (SIWI, Sweden) and Shawview Consulting (UK/Australia), funded by the Swiss Agency for Development and Cooperation (SDC) and other partners. RAMP contributes to the fight against antimicrobial resistance by showcasing good practice in manufacturing and procurement that can mitigate the risk of manufacturing waste streams to provide conditions where bacteria are exposed to selective concentrations of antibiotics. The platform provides a unique multi-sectoral partnership aspiring to broaden the collaboration with governments, industry, international organizations and stakeholders in different geographies and fields of specialization. RAMP aims to turn prevention of antibiotics manufacturing emissions into a business objective by bridging the supply and demand side perspectives to create incentives for transparently implementing improved practice.

Why a RAMP framework?

The RAMP framework provides an independent set of criteria and toolbox of options for responsible manufacturing to reduce the risks of AMR. It takes into account the different perspectives of relevant stakeholders and range scientific and technological options, whilst keeping the main objective as minimising the exposure of environmental bacteria to selective concentrations of antibiotics from manufacturing waste streams. The framework harmonizes individual approaches by different stakeholders, including a voluntary industry standard suggested by the AMR Industry Alliance, scientific publications, procurers and regulators.

Who is the framework for?

The RAMP framework is intended for use by procurers, regulators, local and national governments, pharmaceutical companies and industry groups who want to adopt harmonized criteria that go beyond the current voluntary commitments of the industry, and for other stakeholders such as non-governmental organizations, academics, investors, and antibiotic manufacturers who are a part of the ecosystem that define the enabling conditions for the industry.

While the original scope is on antibiotics, the RAMP framework can be adopted for antimicrobials and pharmaceuticals in general.

2. Status Quo

2.1 Antibiotics and AMR in the environment and the role of manufacturing

To lead the fight against antimicrobial resistance (AMR) there is a need for action from different areas including, but not limited to, development of new types of antibiotics, improved diagnostics, reliable access to antibiotics when needed, and antimicrobial stewardship to prevent the spread of infections by resistant bacteria in the society and ecosystems. In accordance with the One Health Approach, interventions should include human, animal and environmental health aspects.

The largest share of antibiotics reaching the environment comes from usage[1] (for humans and animals) and improper disposal of medical waste and unused medicines. Prudent usage and medical waste management are therefore essential parts for the fight against AMR. While the drivers of AMR related to usage of antibiotics are highly relevant and more likely contribute through the spread of already resistant bacteria, preventing the direct emissions of active pharmaceutical ingredients (API) is important to minimize triggering new resistance, especially in the manufacturing waste streams. [2] Addressing this source of antibiotics to the environment is actionable with the right incentives and implementable regulations.[3]

Numerous scientific studies from several countries have shown that the waste streams from antibiotic manufacturing contain high concentrations of the active pharmaceutical ingredients[4] [5]. At high enough but not inhibitory or lethal concentrations, resistant bacteria (pathogenic or non-pathogenic) have an advantage of being resistant to antibiotics compared to susceptible bacteria (selective concentration). Accordingly, environments with high antibiotic pollution

[1] Laxminarayan R, et al. Antibiotic resistance-the need for global solutions. Lancet Infect Dis. 2013;13(12):1057–98.
[2] Karkman, A., Pärnänen, K. & Larsson, D.G.J. Fecal pollution can explain antibiotic resistance gene abundances in anthropogenically impacted environments. Nat Commun 10, 80 (2019).
[3] Nijsingh, N., Munthe, C. & Larsson, D.G.J. Managing pollution from antibiotics manufacturing: charting actors, incentives and disincentives. Environ Health 18, 95 (2019).
[4] Cardoso O, Porcher JM, Sanchez W. Factory-discharged pharmaceuticals could be a relevant source of aquatic environment contamination: review of evidence and need for knowledge. Chemosphere. 2014 Nov; 115:20-30.
[5] Bielen A et al., Negative environmental impacts of antibiotic-contaminated effluents from pharmaceutical industries. Water Res., 126, (2017).

can provide such selective conditions and serve as incubators for antibiotic resistance[6] [7].

An important characteristic of this risk is that while the antibiotic pollution and exposure is localized in certain hotspots, the APIs are of less concern once the selection for resistance has occurred. The antibiotics might be diluted or degraded, but the resistance remains and can spread geographically and from environmental bacteria to pathogens.

Determining the threshold concentrations of when carrying a gene for resistance is a selective advantage largely follows the logic of ecotoxicological risk assessments, using a so called Predicted No Effect Concentration (PNEC). Concentrations lower than PNEC are assumed to not provide selective conditions. Given the lack of standardized methodologies, the AMR Industry Alliance (AMRIA) suggests combining toxicology (PNEC-ENV) and selectivity (PNEC-MIC) based values in order to use the lower one as the target value. As not all antibiotics have established and published PNEC values, AMRIA also suggested a default PNEC of 0.05 µg/L to be used as the target value[8].

This type of risk assessment is the foundation for the mitigation strategy of ensuring that concentrations do not exceed these PNEC values. Mostly, the comparison is made to Predicted Effluent (or Environmental) Concentration PEC that should be lower than PNEC, often calculated as the Risk Quotient, RQ=PEC/PNEC to be less than 1[9]. For industry effluents, the PEC-value is usually modelled based on the mass balance and calculated loss of the manufacturing process[10].

2.2 Current gaps and challenges in addressing the manufacturing aspect of AMR

There is currently no regulation, in any country, specifically to limit the entry of antibiotics or pharmaceuticals to the environment (neither from manufacturing nor from any other source). In addition, there is little, if any, systematic monitoring for

[6] Bengtsson-Palme, J. et al., Industrial wastewater treatment plant enriches antibiotic resistance genes and alters the structure of microbial communities. Water Res., 162, (2019).
[7] Larsson, D.G.J., Flach, CF. Antibiotic resistance in the environment. Nat Rev Microbiol 20, 257–269 (2022).
[8] AMR Alliance Science-Based PNEC Targets for Risk Assessments (Accessed: 23 March 2023)
[9] Peake, B. et al., 5 - Impact of pharmaceuticals on the environment, The Life-Cycle of Pharmaceuticals in the Environment, Woodhead Publishing, 2016, pp 109-152.
[10] Consolidated PEC/PNEC Calculator Tool for Assessing API discharges (Accessed: 28 March 2023)

the emissions of antibiotic substances since the analytical method Liquid Chromatography-Mass Spectrometry (LC-MS) is not easily accessible in these locations where the hotspots are. This limits the available data largely to scientific studies which confirm that antibiotics can be detected basically anywhere on the globe, and at a broad range of concentrations[11].

The combined lack of regulation and monitoring makes it difficult to attribute pollution in waterbodies to single sources and establish the magnitude of the problem. This, in turn, is a barrier in the various approaches of stakeholders, including industry, procurers, investors etc (see next section) who have been looking for applicable criteria or benchmarks, creating a deadlock between the combined lack of data, criteria and incentives for improved industry practice.

There are specific gaps when it comes to the risk assessment based on the RQ < 1 principle:

- Assuming a certain default PNEC value when substance specific data is missing implies a risk (the precautionary principle would suggest not emitting anything until safe discharge levels are established). Better data-informing default values and providing substance-specific limits would be important gaps to fill.

- PEC must be applied at any point of exposure to bacteria. Depending on the waste streams, this can be in a treatment plant, in the effluent pipes etc. Currently, there is no coherence in this.

2.3 Current approaches to limit API discharge

Various stakeholders are developing and implementing their own approaches to tackle AMR in their spheres of influence. This section provides a comparative overview and gap analysis of these initiatives as the foundation to defining a common denominator and universally applicable criteria.

2.3.1 Pharmaceutical Industry

The Inter Associations Initiative "Pharmaceuticals in the Environment Task Force" comprised of three main pharmaceutical associations in Europe co-founded the

[11] Wilkinson J. et al, Pharmaceutical pollution of the world's rivers, PNAS 2022 Vol. 119 No. 8

Eco-Pharmaco-Stewardship and has published a comprehensive Responsible Manufacturing Effluent Management technical guidance document[12].
The Pharmaceutical Supply Chain Initiative (PSCI) which is a non-profit business membership organization promotes responsible supply chain practices including environmental sustainability, through incorporating what is known as the PSCI Principles in the members' business operations[13]. PSCI conducts trainings to their suppliers on topics such as management of API wastes in manufacturing effluent to help mitigate AMR risks contributed by the industry.
The AMR Industry Alliance (AMRIA), a coalition of pharmaceutical, biotech and diagnostics industries has established a common antibiotic manufacturing framework (CAMF) and the recently formalized AMRIA antibiotics manufacturing standard[14] to minimize the risk of developing antibiotic resistance in the environment from the manufacture of human antibiotics. The signatory companies of the AMRIA are proactively working on reviewing both their own manufacturing and that of their supply chains to assess good practices in controlling releases of antibiotics into the environment. Specific requirements described in the standard to reduce the risk of antimicrobial resistance and the risk of aquatic ecotoxicity in the environment resulting from antibiotics manufacturing operations include:

- Management of antibiotic process wastewater discharges during manufacturing to meet PNEC,
- Methods to minimize the amount and concentration of antibiotics lost to wastewater,
- Handling, treatment, and disposal of other antibiotic waste to minimize or eliminate release of antibiotics into the environment, and
- Processes and systems to demonstrate conformity to local regulations and the AMRIA CAMF and standard.

2.3.2 Procurers

Nordic countries[15] [16] have led the development of sustainability criteria for pharmaceutical manufacturing for many years. In addition, several member states in the EU started establishing their national public procurement strategies and legislation after the EU launched a new updated Directive on Public Procurement[17] that included health, environmental and financial aspects as award criteria for the best economic advantageous tender. UK NHS is also testing a new national

[12] Responsible_Manufacturing_Effluent_Management_Technical_Guidance.docx (efpia.eu) (Accessed: 13 March 2023)
[13] The PSCI Principles - PSCI (pscinitiative.org) (Accessed: 13 March 2023)
[14] AMRIA_Antibiotic-Manufacturing-Standard_June2022.pdf (amrindustryalliance.org) (Accessed: 13 March 2023)
[15] Sustainability criteria for Medicinal Products | The National Agency for Public Procurement (Accessed: 13 March 2023)
[16] New joint Nordic tendering procedures - Amgros (Accessed: 13 March 2023)
[17] EUR-Lex - 32014L0024 - EN - EUR-Lex (europa.eu) (Accessed: 13 March 2023)

purchasing agreement[18] (subscription-type payment model) using a healthcare technology assessment developed by the National Institute for Health and Care Excellence.

UN agencies joined forces in the UNDP-led inter-agency task team Sustainable Procurement in the Health Sector (SPHS) and collaborated with a group of low- and middle-income countries in the project Sustainable Health in Public Procurement (SHiPP). These initiatives launched the Sustainable Procurement Index for Health[19] that included chemicals (pharmaceuticals specifically) as one of the themes, with criteria that assess the wastewater management and monitoring of water quality (PEC in comparison to PNEC).

2.3.3 Regulators

Regulatory instruments may complement the market incentives and voluntary self-regulation. These include the application of sustainability criteria for antibiotics in generic substitution and reimbursement schemes, subsidies, environmental and pharmaceutical regulation or good manufacturing practice. In most of these fields, there are individual governments or agencies exploring options but equally facing the lack of established standards.

To highlight two examples, on the one hand, the Swedish government is currently assessing options for an environmental bonus[20] in the generic substitution system to incentivize pharmaceutical manufacturers that adopted environmental criteria for the emissions of active substances during manufacturing. This includes antibiotics as a priority, and the project will trial the introduction of environmental premium as part of the procurement.

On the other hand, the Government of India had announced its intention to become the first country in the world to regulate API discharge levels for antibiotic manufacturing. The complications that these efforts ran into are a case study of the complexity and conflicting interests at play.

[18] Models for the evaluation and purchase of antimicrobials| NICE (Accessed: 13 March 2023)
[19] Sustainable Procurement Index for Health: User Guidance (UNDP, 2021) (Accessed: 14 March 2023)
[20] Tillgänglighet till vissa antibiotika (Folkhalsomyndigheten, 2023, Artikelnummer 22283) (Accessed: 14 March 2023)

Box 1: Regulatory efforts in India

India is renowned for its pharmaceutical manufacturing and aims to become a world leader in antimicrobial production. However, high levels of antibiotics found in manufacturing hubs in India have raised concerns about the country's role in the growing problem of antimicrobial resistance. Both the government and industry leaders understand the need to adopt sustainable and responsible practices in antibiotic manufacturing to meet global demand and enhance competitiveness in the international market.

India's environmental regulations have undergone significant changes in recent years and now boast some of the strictest requirements for antibiotics manufacturers. For instance, all API bulk-drug manufacturing facilities are classified as "grossly polluting industries" and must comply with zero liquid discharge (ZLD) standards. In January 2020, the Ministry of Environment, Forest and Climate Change (MoEFCC) proposed standards for the bulk drug and pharmaceutical industry, including antibiotic residue parameters. In January 2022, the Central Pollution Control Board issued new guidelines for monitoring API discharges into the environment. The final standards for the bulk drug and pharmaceutical industry were notified in August 2021, following stakeholder and expert consultations, but the limits on antibiotic discharge were not included. Currently, the matter of regulating the discharge of antibiotic APIs from manufacturing sites is being contested in the courts.

Regardless of the outcome in the Indian courts on the API discharge standards, India remains the only nation with regulations being considered for discharge standards on antibiotic compounds. This highlights the growing regulatory pressure for Indian antibiotics manufacturers to adopt responsible manufacturing practices.

The Central Pollution Control Board has prepared “Guidelines on **Monitoring Mechanism** for API residue” and circulated this mechanism to the State PCBs as directed by the National Green Tribunal in January 2022. The guideline recommends sampling of effluent along with the point of final discharge to assess effectiveness of effluent treatment (p.9). For ZLD facilities, it shall be ascertained that there is no effluent bypassing or discharge by any other means (p.14). And for manufacturing sites discharging treated effluent to inland surface water, monitoring of both treated effluent and the water body shall be conducted. These are part of

the duties of State Pollution Control Boards (SPCB) and Pollution Control Committees (PCC).

The Ministry of Health and Family Welfare (MoHFW) has also taken a step in promoting transparency in the pharmaceutical supply chain by requiring a QR code on the label of all APIs manufactured or imported in India. This change went into effect in January 2023 and allows for the tracking and tracing of ingredients at each level of packaging. Although this does not contain environmental information, it provides an opportunity to match supplier and environmental information or add environmental information to the label at a later stage.

Important references can also be found in environmental regulation like the European Industrial Emissions Directive. The approach here is to define Best Available Technologies[21] to reduce or prevent emissions. There is no such approach systematically applying this to antibiotics or pharmaceuticals, although the recommendation of Zero Liquid Discharge technologies in parts of India follows the same logic of defining the desired intervention rather than the exact outcome. Chemical Oxygen Demand (COD), Total Organic Carbon (TOC) and Biological Oxygen Demand (BOD), among others, are most often the established parameters for regulating wastewater emissions when it comes to organic load. While there is limited data available, some initial studies describe significant correlation between antibiotic residues and water quality parameters[22].

2.3.4 International agencies and other relevant initiatives or stakeholders

UN Agencies: Beyond the UN procurement initiative SPHS (see above), WHO has published a reference document[23] with points to consider for manufacturers and inspectors regarding environmental aspects of manufacturing for the prevention of AMR as part of a Technical Report Series. With this working document WHO is assessing the possibility of including environmental criteria for waste and wastewater management as part of WHO GMP pre-qualifications.

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[21] The Industrial Emissions Directive EUR-Lex - 32010L0075 - EN - EUR-Lex (europa.eu) (Accessed: 14 March 2023)

[22] Hanna N, Purohit M, Diwan V, Chandran SP, Riggi E, Parashar V, Tamhankar AJ, Lundborg CS. Monitoring of Water Quality, Antibiotic Residues, and Antibiotic-Resistant Escherichia coli in the Kshipra River in India over a 3-Year Period. Int J Environ Res Public Health. 2020 Oct 22;17(21):7706.

[23] Annex 6, WHO Technical Report Series, No. 1025, 2020 (Accessed: 14 March 2023)

There are also several references calling for responsible manufacturing in high-level declarations from the Global Leaders Group on AMR (GLG)[24], G7[25], G20[26] and a few AMR national action plans (NAP). However, on this level, there is usually no detail on how this is meant to be achieved.

Investors are also starting to engage with policy makers and portfolio companies to improve practices and promote better risk management. A coalition to form Investor Action on AMR[27] is committed to use their influence as investors to drive R&D investments and antimicrobial stewardship and support interventions under a One Health approach.

[24] https://www.amrleaders.org/about-us (Accessed: 15 March 2023)
[25] G7 Health Ministers' Communiqué, 2022 (Accessed: 15 March 2023)
[26] Declaration of the G20 Health Ministers, 2021 (Accessed: 15 March 2023)
[27] Investor Action on AMR (Accessed: 15 March 2023)

3. The need for independent and harmonized criteria

As described above, there is a multitude of strategies and methodologies, driven by stakeholders to mitigate AMR risks in their respective scope. The lack of a broadly accepted framework to address pollution from antibiotic manufacturing implies that these risks might not be addressed sufficiently or come at the price of inefficiencies, prohibitive costs and burden of compliance control. This, in turn, could put parts of the supply chain at risk.

Preventing this requires harmonized and coherent policy changes that enable and empower the relevant stakeholders to live up to their responsibility in demanding, incentivizing, or implementing improved manufacturing practice with available solutions and acceptable effort.

The industry-led AMRIA Antibiotic Manufacturing Standard[14] is currently the only tangible standard that is referred to by several political pledges or calls. It provides a natural starting point for a harmonized standard that would be applicable also to meet the needs of other stakeholders and act as an interface to define criteria and exchange information between the involved parties. To achieve this, some key constraints that limit widespread adoption need to be addressed:

1. The concentration centered approach (PNEC) is not correlated with existing parameters in environmental regulation (BOD/COD/TOC etc.), limiting the applicability for important existing policy instruments.

2. The standard compares PEC to PNEC in the mixing zone. This is questionable as it does not exclude exposure of bacteria to antibiotics at selective high concentrations before dilution is achieved.

3. Compliance is not directly verified through measurements but based on combining two complex models: Mass balance to calculate for the estimated losses of API during the manufacturing process, and hydrological data to calculate the dilution. Although applying risk margins on several levels, this leaves verification to a high level of abstraction.

4. The AMRIA antibiotic manufacturing standard is an industry-led initiative and scaling it beyond an initial level to ensure that all manufacturers

globally are compliant is a key challenge that requires broader ownership and governance.

A key challenge in any future standard is the verifiability of compliance. Partly, this is due to the lack of transparency about supply chain details in the pharmaceutical industry. The other challenge is the data itself: as long as direct sampling measurements of API concentrations are costly and only provide a snapshot in time, there is a need for proxies that indicate compliance with safe discharge limits by other methodologies. This can be achieved by:

- Modelling concentrations (as suggested by the AMRIA)

- Prescription of specific interventions or technologies (as applied by some state governments in India, and in the European Industry Emissions Directive (although currently not for regulating API emissions).

- Qualitative prescription of specific management practices like Environmental Management Schemes (partly adopted in the AMRIA standard)

An independent framework would be required to synthesize and connect the needs, limitations and applicability of the different methodologies that several stakeholders have already initiated, as outlined in section 2.3.

4. The RAMP Framework approach

To provide such a framework, addressing different stakeholders' roles and needs, the Responsible Antibiotics Manufacturing Platform (RAMP) **builds on the improved industry practice (AMRIA standard)** from the private sector, and **integrates government agency policies, scientific data from academia** and other relevant organizations to **create an enabling environment for improved industry practice**.

The main objective is to **prevent exposure of bacteria to selective concentrations of antibiotics from manufacturing waste streams**.

Key principles to define harmonized criteria for responsible antibiotic manufacturing

4.1 Scope and rationale for criteria

Compliance with the core objective of preventing selective concentrations ultimately requires physical measures to control API emissions. As outlined above, verifying this can be difficult. Thus, this RAMP Framework suggests allowing for different methods, levels of commitment and means of verification to ensure that antibiotics are produced responsibly.

The flowchart below illustrates the overall idea of the framework approach. It takes into account the assessment flows for an antibiotic API manufacturer or for a company formulating the finished product or a distributor. Two alternative tracks are suggested to be included as a component in a company's environmental management system to ensure that the manufacturing waste stream is not a point of exposure for selection of resistant bacteria. Lastly, an assessment matrix for the final output (i.e. water quality or solid waste disposal) is presented, with suggested recommendations on what is acceptable and not acceptable. A detailed explanation of these processes and decision points follows.

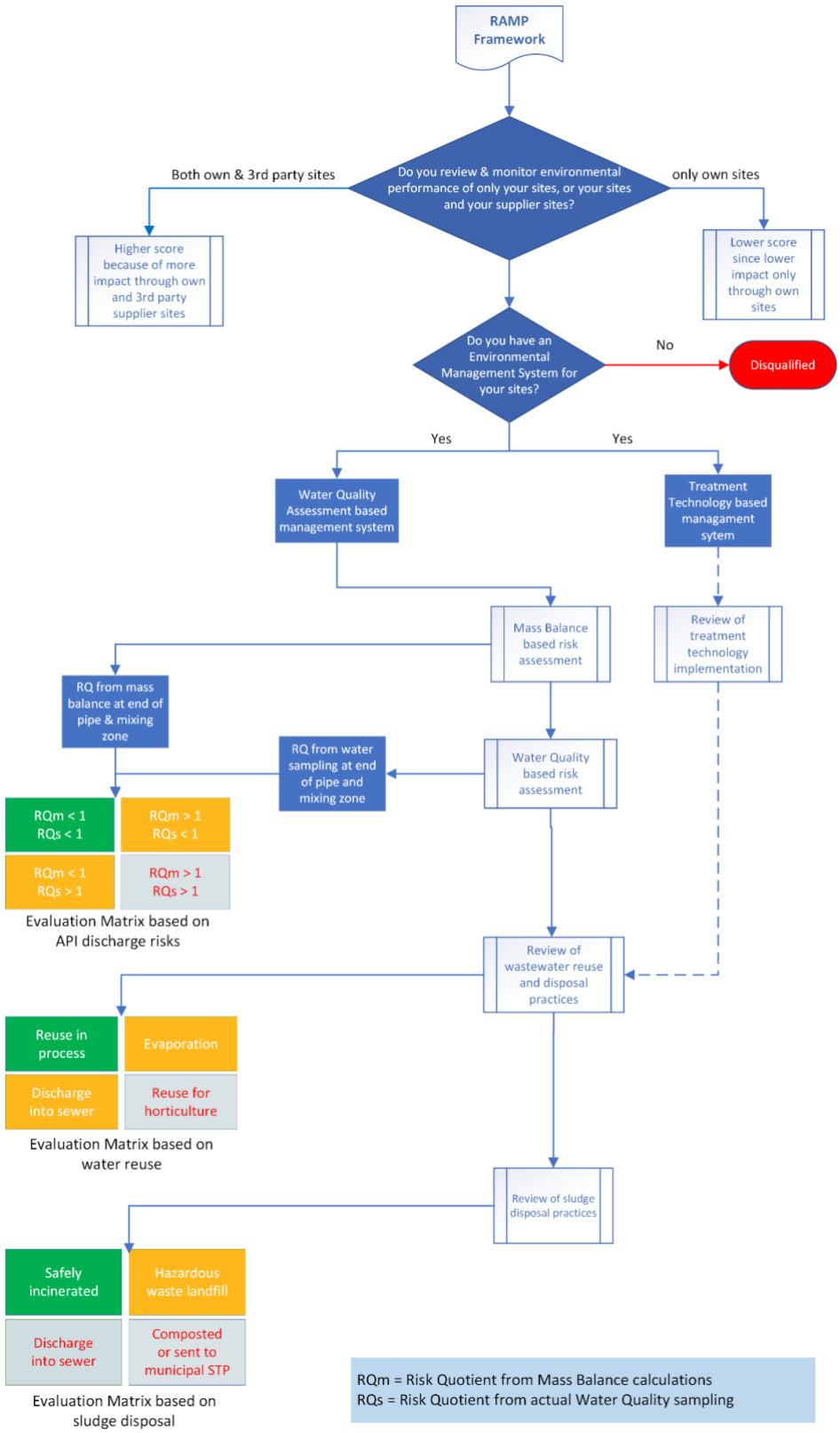

Figure 1. The RAMP Framework approach

4.1.1 Qualitative assessment

Having a comprehensive **environmental management system (EMS)** in the manufacturing facility is an effective way to implement processes and procedures that help the organization not only to increase their operational efficiency but also to ensure that environmental performance from their operations is continuously reviewed, evaluated, and improved. This includes defining roles and responsibilities, training and education, and target follow-ups such as measurement, monitoring and (self) auditing. The most used framework for EMS is the ISO 14001 standard which is based on a Plan-Do-Check-Act method. When API emissions are identified as a risk, adequate mitigation strategies are mandatory. Although these objectives and targets are set by each individual organization's EMS, demonstrating **concrete policies for including management and control of API emissions and documented implementation** elevates their level of commitment to guarantee that the facility is responsibly manufacturing antibiotics. This level of assessment gets maximum incentive if the facility follows the criteria for EMS set out by ISO 14001 and has a valid certificate for it.

4.1.2 Water quality (Quantitative assessment based on API concentrations)

This approach is centred on the PEC (predicted environmental concentration) of the API in the effluent stream in comparison to the PNEC (predicted no effect concentration) as targets established by the industry and academia. The most accurate way of determining this value is through **direct measurement** of a water sample and determining the API concentration through LC-MS which is currently the only established and accepted analytical standard. Timing of sampling needs to correspond to the nature or schedule of production. An alternative method adopted by the AMRIA is to estimate the loss of API from the manufacturing process by **mass balance calculations and model** the concentration of the API in the environment, taking into account the hydrological conditions in the local area.

Both methods allow for determining the level of risk to the environment, with RQ < 1 being the acceptable value. However, there can be two stages of defining the PEC value – the first one being the **PEC value from the mixing zone of the receiving water body** (i.e. after applying a conservative dilution factor), and a more stringent **PEC value calculated or measured at the point of emission** (applies either to the facility or to a CETP receiving API waste streams).

These compliance levels have their own limitations. Assessing the RQ in the mixing zone makes it difficult to identify the specific manufacturing facility in the local area that potentially discharges high concentrations of API in their waste stream. This is

problematic since there is already a risk of exposing bacteria to high selective concentrations from the point of emission to the mixing zone. On the other hand, taking a water sample at the point of emission for factories that implement Zero Liquid Discharge technology would not be applicable. This is addressed in the technology-based method that follows.

4.1.3 Technology or intervention-based

This approach lifts the burden of proof from modelling or measuring micro molecular concentrations to allowing a proxy which assumes that **by applying certain technological or process interventions, manufacturing waste streams should be able to comply with RQ < 1 at the point of emission**. Performance and efficiency of the technologies to be implemented are the key components in achieving this and defines what types of interventions can be regarded as sufficient.

Zero Liquid Discharge is probably one of the most implemented approaches (at least in India where it is a requirement) to treat wastewater effluents for the pharmaceutical industry. It is a very effective process in removing impurities after primary and secondary treatment since the water passes through a reverse osmosis membrane, allowing only pure water to pass through it. This concept means that final wastewater streams can then be used for other purposes such as in facilities equipment like boilers and cooling towers. In terms of sustainability, there is a trade-off with high energy demand and water not being re-used for the process or returned to the waterbody.

Advanced Oxidation Processes (AOPs) as a tertiary step in wastewater treatment are very effective in degrading chemicals including those that are recalcitrant compounds. The most widely applied techniques are ozonation, UV photo-oxidation, plasma oxidation or the use of catalysts in a reactor to generate highly reactive oxidants that are then utilized to degrade the organic pollutants present in the system. Advanced oxidation combined with activated carbon or sand filters have been successfully applied in some wastewater treatment plants as a final treatment step in removing pharmaceutical residues. Even here, implementation implies higher energy demand.

Evaluating which intervention is the most cost- and resource-efficient to implement in a manufacturing plant is rather dependent on the properties of the APIs produced, incoming concentrations and other considerations (cost of electricity, infrastructures, regulatory requirements etc.). There are accessible databases for

different technologies that deal with pollution and waste (wastewater treatment) such as the one maintained by the US EPA[28] as well as WIPO Green[29].

Another alternative intervention which offloads the burden from the manufacturer to guarantee that no harmful levels of APIs are discharged from the facility is to subcontract handling of **wastewater treatment as a service (WaaS)**. The client defines and specifies what the wastewater treatment objectives are, and the service provider then designs the system and strategy for achieving the performance that is required and ensures that the specifications are achieved and monitored regularly to enable transparent and verifiable reporting.

To verify compliance, **proxy water quality parameters** such as COD, TOC or UV254 can be used for both concentration- and technology-based interventions. They are well established and usually required by regulations to quantify organic matter in water. Establishing a scientific correlation between the API concentration and COD level of each specific compound that a facility produces would allow for a simple and accurate indicator. A suggested parameter for compliance could then be for instance requiring a certain percentage of **COD reduction** from the inlet to the outlet.

Solid wastes and salts potentially containing API residue need to be classified and disposed of in accordance with local regulatory requirements. This applies also to third party contractors who manage the final treatment and/or disposal of these wastes with hazardous characteristics. Specifically authorized incineration or landfill disposal sites must have monitoring programs to avoid occurrence of potential leaks or seepage of waste materials into the environment.

4.2 Reporting

Validating compliance with any of the above approaches requires adequate data and capacity to analyse the information. This responsibility is either on the supplier, the buyer or it can be outsourced to a third party. The RAMP Framework suggests the following levels:

Self-reporting is a good start and requires the responsible persons to be proactive in discovering deviations from the objective, documenting and correcting them, and making sure that corrective actions are in place to prevent recurrence of the problem.

[28] Industrial Wastewater Treatment Technology Database, US EPA (Accessed: 15 March 2023)
[29] WIPO Green Database of Innovative Technologies and Needs (Accessed: 15 March 2023)

Sharing reported data through industry association reports, annual company reports, or independent benchmarks allows other stakeholders to assess the general level of performance within the industry. Access to such data can help buyers or regulators to differentiate between suppliers but requires adequate resources to process and interpret the information.

To ensure credibility and quality of reported results and reduce burden on both sides for providing and analysing information, a **third-party review and validation** (i.e. by means of certification) would be the highest level of validation of compliance that enables procurers and regulatory bodies to determine if the manufacturer is meeting the objective of not contributing to the drivers of AMR. An accepted certificate can also be shared with different stakeholders to avoid repetitive processes.

4.3 Procurement Tool

Based on the above methodologies and voluntary reporting mechanism, the RAMP Framework provides a questionnaire that allows manufacturers and suppliers to do initial self-assessment (See Annex 1). The answers to the questionnaire can serve as the interface for governments, funders and procurers to evaluate the level of commitment and achievement of the supplier/manufacturer and will guide them in awarding incentives during the tendering process. The tool operationalizes the logic of the flowchart (see Figure 1) through a scoring mechanism that can be weighted along the needs and priorities of the buyer and depending on the answers clarifies the information that the supplier needs to provide.

5. Remaining challenges and limitations

For all the general approaches described, technical solutions are commercially available, and some frameworks are established. But they also come with their specific challenges of how compliance with the criteria is verified, as well as cost implications and trade-offs with energy consumption associated with implementation and verification. Overall, this has to be seen as a combined technical-scientific, funding and governance challenge.

5.1 Means of verification

Considering the low threshold values of PNECs and the sheer number of API manufacturing sites, direct sampling as means of compliance control is challenging given the limited analytical laboratory capacities and currently high costs. In addition, it only allows for ex post verification and at the risk of missing short emission peaks. Furthermore, measuring for compliance in the mixing zone makes it impossible to attribute detected concentrations to sources.

Automated real time measurements would be the optimal monitoring solution and are currently being developed but not yet commercially available. Optical sensors with the aid of artificial intelligence (big data) might be able to estimate concentrations directly in the effluent where the expected molecules and expected concentrations are known and allowing for sensors to be calibrated without complicated interference. The Shanghai municipal government in China has recently included antibiotic manufacturers in its requirements for industrial manufacturing firms to provide electronic emissions data to local government regulators in real time.

Proxies based on prescribing specific technologies or management practice lift the burden of proof from molecular concentrations to a macro level. In turn, this calls for stronger governance defining what types of interventions or technologies can be regarded as sufficient. However, there are no Best Available Techniques (BAT) reference documents (BREF) yet that cover monitoring parameters applicable for the pharmaceutical industry. This BREF for the pharmaceutical sector could be developed and implemented to prevent antibiotics emissions from manufacturing.

Environmental Management Systems (EMS) require an assessment of environmental risks in manufacturing, making adequate mitigation strategies mandatory once a risk (e.g. API emissions) is identified. The level of environmental

performance, however, is not dictated in the EMS since this is designed in accordance with the organizations' individual objectives and targets.

5.2 Governance and ownership

Despite the pioneering character of the AMRIA standard, it provides a fundamental governance challenge to be solved for any approach or standard to be broadly adopted. Who is or should be in-charge of regulation and setting the general frame in:

- Defining and updating PNEC values
- Defining and updating Best Available Technologies and BREF.

Overall implementation in manufacturing will not happen without clear regulatory demands – these are co-requisites. To achieve this, a level playing field and transparent demands and conditions are essential, manifested in coherent policy and market instruments. This Framework aims to serve a foundation to harmonized and universally applicable criteria for different kinds of users and purposes. As with many industry-derived standards and codes, potential issues concerning the AMRIA standards could include universality, verification, enforcement, and scope for maintaining ongoing relevance in the context of evolving scientific evidence and community standards.

5.3 Cost of compliance vs cost of inaction

A key challenge is the limited understanding of costs of action vs inaction and the possible impacts of both (see Table 1). The scenario outlined in the table shows that the ultimate cost of changing practice materializes almost entirely on the local manufacturing level – leading to the risk of disrupting supply chains[30]. However, this is based on the assumption that the local manufacturer is left alone with these costs in a market with severe price pressure.

In an alternative scenario, locally reduced pollution and global mitigation of AMR risks are public interests that are adequately priced through coherent market instruments (i.e. rewarding improved practice). The attempts of a growing number of procurers, investors and regulators to achieve this, demonstrates a general willingness to pay and subsidise the costs of action for manufacturers in the interests of improving environmental, global health and business competitiveness

[30] Wellcome Trust, Boston Consulting Group; "Understanding the antibiotic manufacturing ecosystem", 2022.

outcomes. For example, the Kanartaka state government in India's most recent industrial development policy includes providing government grants to local manufacturers to subsidise the costs of implementing antibiotic pollution control measures.

A key challenge in designing such incentives adequately, is a better understanding and transparency of costs of practical implementation and verification. Supporting this logic, there is also a need to better understand the costs of inaction or, in turn, the value of mitigating risks from antibiotics pollution from manufacturing both from the environmental and health perspectives.

	Cost of Action	Possible Impact of Action	Cost of Inaction	Possible Impact of Inaction
Local suppliers	Investments in new practices and technologies	Rising capital expenses and operational costs	Failure to invest in new practices and technologies	Vulnerable to regulatory change and competitiveness, loss of markets and customers
Local communities	n/a	Loss of livelihood opportunities? Less AMR Clean environment	n/a	High degree of contamination – affects human and env. Health
Pharmaceutical brands	n/a	Loss of profit/market shares in short term? Brand value	n/a	Reputational damage; Missed opportunity to be an early mover
Global Health systems (Regulators and procurers)	Possible higher prices for antibiotics, disrupted supply chains	Rise in costs of medicine or limited access? Reduced AMR risk	Higher prices and/or supply chain problems; increased health system costs	Rising healthcare costs and human fatalities, new drug-resistant pathogens and epidemics/pandemics
Investors	n/a	Loss of profit in the short term? Investment opportunity	n/a	Financial risks; lower commercial returns; Reputational damage

Table 1: Distribution of costs and impacts of action vs inaction among different stakeholders along or impacted by antibiotic manufacturing and markets. This shows a scenario where the local manufacturer is left alone with the investments, leading to positive effects (light blue) including the mitigation of AMR risks but also implying risks to the market (dark blue), including reduced competitiveness, losing job opportunities, and impacting the global supply.[31]

However, as with many global environmental, health and business issues, a key challenge here is also to understand the costs of *inaction* in dealing with antibiotic pollution. While the costs of acting on antibiotic pollution may be more easily identified (and sometimes opposed), the costs of inaction are often more intangible but extensive in the long run.

[31] Adapted from Rudebeck, Schaaf et al. Combatting antimicrobial resistance (AMR) by managing environmental contamination in antibiotic manufacturing (2021) unpublished discussion paper, Stockholm International Water Institute

No action on addressing antibiotic pollution from its sources, including the potential pollution risks from the manufacture of antibiotics, is increasingly identified as a major global environmental and health risk for the world. Local communities may experience growing susceptibility to drug-resistant infections, but the risks for the global population in being susceptible to new drug-resistant pathogens, including bacteria and other microbials, increase. As demonstrated by the recent Covid-19 pandemic, the social and economic costs of inaction can be substantial for countries, governments, business and the community.

Various reports have identified the future human, environmental and economic cost of inaction on AMR more generally. To varying degrees antimicrobial pollution in general, including antibiotic/antimicrobial manufacturing, is likely to be a contributing factor to the global AMR risk.

6. Conclusions and future needs

Triggering antibiotic resistance through exposure of bacteria to high concentrations of antibiotics in manufacturing waste streams is a risk with no upside – except for the need of suppliers to respond to the price pressure in the generic antibiotics market. There are different collaborations and efforts to address this challenge both locally and globally. However, most of these initiatives are still too fragmented to have a significant systematic impact.

The underlying physical objective is straightforward, and technical solutions do exist. Nevertheless, a common understanding of what to achieve and how to verify compliance is essential in order guide decision making and technology deployment. This common understanding will be much more effective if it can be achieved through agreement across a range of stakeholders including governments, regulators, funders, industry, international organisations, scientific and policy experts, environment groups and the broader community.

There are missing links stretching all the way from the scientific foundation of antibiotic pollution, through adequate technologies, to coherent policy and market instruments. Addressing these will empower stakeholders to interact on a level playing field and act according to their respective responsibility and possible impact:

1. Science-based targets: PNEC values have been established for many antibiotic compounds but there is a need for widespread and impartial ownership and continuous review through an international expert panel. This could be hosted under WHO or the Quadripartite for AMR.

2. Defining Best Available Technologies: The guidance through BREF documents would be a key in translating the science-based targets into appropriate technical measures. This would provide a critical interface between what the demand side is asking for and demonstrating compliance. The ownership of BAT and BREF documents needs to be with an independent international organization, possibly in conjunction with the scientific expert panel or through an organization like OECD who has experience with comparable instruments.

3. Improving monitoring capacity: Even when working through proxies like BAT, environmental monitoring and verification through water quality parameters needs to be part of the equation. On the one hand, laboratory

capacity needs to drastically increase, likely also serving for a scaling effect that reduces sampling costs. On the other hand, new technologies e.g. optical sensors for real time monitoring can significantly improve and simplify compliance control. Monitoring in this context also needs to include antibiotic resistance genes as those are the ultimate risk that persists even after APIs might have been diluted or degraded.

4. A collaboration platform should bring together practitioners from all relevant stakeholder groups in order to raise awareness about the scientific needs and corresponding market demands and opportunities, improve access to existing knowledge and solutions, and support technology development through pilots and testbeds.

Collaboration: Learning and moving forward in mutual responsibility and accountability

To address the above gaps and challenges in governance and ownership, stakeholders must collaborate more than they do today. To ensure environmental management in the most effective way and without massively increasing administrative burdens and paperwork for both procurers and suppliers, a common framework is needed, bridging between the varying perspectives and approaches of various procurers, regulators and the voluntary commitments from industry through the AMRIA and other business groups. This needs to be complemented with a practical mechanism (e.g. procurement questionnaire) for demonstration and verification of the steps taken by the manufacturers and suppliers to reduce / eliminate the impact of manufacturing on AMR.

Considering that no single solution fits all and that no global regulatory governance is yet established, the RAMP Framework assesses the available methodologies and makes these accessible for **voluntary implementation**. This allows stakeholders from supply and demand side to harmonize their efforts, develop mutual leverage rather than friction and pave the way for procurers to **incentivize** manufacturers and suppliers who do better. Cross-sectoral collaboration provides opportunities to overcome growing environmental problems, address emerging global health threats, develop more efficient businesses and create new commercial opportunities.

RAMP suggests this framework to be adopted by key stakeholders including procurers, regulators, and manufacturers. Experience from this work should inform the review and further spread of the methodology through an **informal global collaboration platform**.

In addition, a physical collaboration centre for capacity building, knowledge and technology sharing and testbed facility should complement the implementation of the Framework. Such a **RAMP Centre of Excellence** (CoE) should lead industry, government and regulatory transformation towards responsible antibiotics manufacturing and maintain competitiveness. The CoE would focus on:

1. Providing a multi-stakeholder platform for spreading awareness and advancing collaborative action for the fight against AMR through academic trainings.

2. Capacity building and addressing the training needs of various stakeholders.

3. Supporting the creation of infrastructure for testing and treating antibiotics. This could include analytical and microbiological laboratory for water quality assessments as well as testbed facilities for verifying and testing new monitoring and treatment technologies.

4. Support BAT/BREF development through pilot projects, databases and in close dialogue with the global collaboration platform.

Implementing the Framework in these ways, supported and coordinated through a global platform and a Centre of Excellence should be complemented through an expert advisory board to ensure scientific rigor and review. Such an ecosystem of voluntary partnerships among early movers could pave the way towards broader harmonization, standardization, ownership and governance of the approach.

The ultimate goal is to ensure science-based targets that guide industry practice, supported through harmonized, coherent and efficient policy and market instruments. An international standard for responsible antibiotic manufacturing, based on this approach, could inform procurement, environmental regulation, Good Manufacturing Practice etc. – which, in turn, would support scaled, industry wide implementation.

Such harmonization is assumed to not only strengthen the market for technical solutions and monitoring, including the creation of marketplaces or matchmaking tools, but also the generation of investment support for the industry to become compliant. Transparency about costs and benefits of interventions will play an important role in supporting decision making on both supply and demand sides.

List of Abbreviations

AMR	Antimicrobial Resistance
AMRIA	AMR Industry Alliance
API	Active Pharmaceutical Ingredient
BAT	Best Available Technology
BOD	Biological Oxygen Demand
CAMF	Common Antibiotics Manufacturing Framework
CETP	Central Effluent Treatment Plants
COD	Chemical Oxygen Demand
CoE	Centre of Excellence
EMS	Environmental Management Systems
GLG	Global Leaders Group
GMP	Good Manufacturing Practice
LMIC	Low- and Middle-Income Countries
MoEFCC	Ministry of Environment, Forest and Climate Change
MoHFW	Ministry of Health and Family Welfare
NAP	National Action Plan (on AMR)
PCC	Pollution Control Committee
PEC	Predicted Environmental Concentration
PNEC	Predicted No Effect Concentration
PSCI	Pharmaceutical Supply Chain Initiative
SPCB	State Pollution Control Board
SPHS	Sustainable Procurement in the Health Sector
SPIH	Sustainable Procurement Index for Health
TOC	Total Organic Carbon
ZLD	Zero Liquid Discharge

About this publication

The Responsible Antibiotics Manufacturing Platform (RAMP) Framework provides a customisable set of guidelines and independent criteria to evaluate a supplier for responsible antibiotics manufacturing. RAMP is hosted by Stockholm International Water Institute (SIWI) and implemented together with Shawview Consulting and Spans Envirotech. The project was mainly financed by the Swiss Agency for Development and Cooperation (SDC).

Authors

This paper has been authored in 2023 by Iris Panorel, Nicolai Schaaf, Nitin Verma, Brendan Shaw, and supported by Siddhartha Prakash and Kia Salin. Any inaccuracies remaining in the text are entirely the responsibility of the authors.

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Annex 1. RAMP Framework - Procurement Questionnaire (Sample)

Supplier Name	Example supplier	**SHORT DESCRIPTION**
Date	(17-Nov-2022)	Example Buyer
Site Name	Example Site	
Tender Ref	Tender #123	
Country	Example country	
Review Led by:		

SAMPLE

Overall Summary Score

WHO AWaRe Classification of Antibiotics: Reserve

	Raw Section Score	Maximum Section Score	Weightage	Weighted Score	
Section 1 - Environmental Management System	20	20	10%	10,0	Score range: 0 to 20
Section 2(a) - Waste Management Processes of Tenderer	30	40	20%	15,0	Score range: 0 to 40
Section 2(b)- Waste Management Processes of Tenderer's API/Chemical Manufacturer	50	50	20%	20,0	Score range: 0 to 50
Section 3 - Verification	110	165	40%	26,7	Score range: 0 to 165
Section 4 - Other Matters	30	40	10%	7,5	Score range: 0 to 40
Total Score for ranking	240	315	1,00	79,2	

Section 1 - Environmental Management System		Instructions / Guidance	Required Evidence	Supplier Reference Document and Comments
Does the company have an environmental management system (EMS) in place? (Yes or No)	Yes		Please share your EMS document.	see attached file_name1.pdf
Is the EMS independently certified/reviewed (i.e. ISO certification)?	Yes		Please share certificate and date of validity.	
Does the company report to a voluntary scheme to disclose environmental performance?	Yes		Please share link to report/scheme document.	

Section 2(a) - Waste Management Processes of Tenderer			Required Evidence	Supplier Reference Document and Comments
On Site Treatment				
Does the manufacturing site have an onsite effluent wastewater treatment / Effluent Treatment Plant (ETP) that meets the minimum local regulations?	Yes		Please share copy of onsite treatment permit.	
Is your ETP based on a certified/industry accepted Best Available Technology (BAT) for treatment of pharmaceutical wastewater?	Yes		Please specify tertiary treatment technology.	
Off Site Treatment				
If you do not have onsite wastewater treatment plant, do you send your manufacutring wastewater to an industrial wastewater treatment plant / combined	Not Applicable			
Is the off-site wastewater treatment plant / CETP based on a certified/industry accepted Best Available Technology (BAT) for treatment of pharmaceutical	Not Applicable			
Has the third-party provider shown proof of compliance to local regulations?	Not Applicable			
Do you have and track the performance of the CETP?	Not Applicable			
Wastewater Reuse and/or Discharge				
Do you discharge any of the untreated or treated wastewater from your manufacturing facilities into a waterbody (eg. lake, river, ocean, groundwater etc)	Yes		Please share copy of a valid waste disposal authorization	
Do you discharge any of the untreated or treated wastewater from your manufacturing facilities into a public sewer?	No			
Do you reuse any of the treated wastewater for utilities (eg. process, cooling tower, boiler etc)?	Yes		Please indicate estimated reuse percentage	50%
Do you reuse any of the treated wastewater for horticulture, gardening?	No		Please share a declaration on your letter head.	copy of letter
Sludge and Rejects Management				
Where is the sludge from your wastewater treatment plant disposed?	Hazardous Landfill		Please share copy of a valid waste disposal authorization letter/permit.	

Section 2(b)- Waste Management Processes of Tenderer's API/Chemical Manufacturer			Required Evidence	Supplier Reference Document and Comments
How many manufacturers are going to be involved in supplying API in relation to this particular tender?	5	*Enter whole number between 0 and 100*	Please provide a list of suppliers.	
What portion of your suppliers environmental performance do you monitor on a regular basis?	All Suppliers			
Do all of your suppliers possess authorization to discharge treated effluent?	Yes			
Do any of your suppliers discharge any of the untreated or treated wastewater from your manufacturing facilities into a waterbody (eg. lake, river, ocean,	No			
Do any of your suppliers discharge any of the untreated or treated wastewater from your manufacturing facilities into a public sewer?	No			
Do any of your suppliers reuse any of the treated wastewater for utilities (eg. process, cooling tower, boiler etc)	Yes			
Can you confirm that none of your suppliers reuse any untreated or treated wastewater for horticulture or gardening?	Yes		Please share a declaration on your letter head.	

Section 3 - Verification			Required Evidence	Supplier Reference Document and Comments
On Site				
Do you conduct a mass balance on the expected/modeled API discharges in your wastewater?	Yes			
What is the frequency of conducting mass balance studies for the proposed antibiotic(s)	Batch			
What is the RQ (= PEC/PNEC) value based on mass balance in your effluent water (at the end of the pipe/outlet from your manufacturing site)?	0,9	*Enter RQ between 0 and 10 (eg. 0.7 or 1.5)*	No supporting calculations need to be submitted at this time. Supporting evidence may be sought in the future.	
Do you measure/monitor APIs concentration in your effluent water (at the end of the pipe/outlet from your manufacturing site) prior to discharge or reuse?	Yes			
What is the frequency of conducting water quality sampling and testing for the proposed antibiotic(s)	>1 year			
Do you compute and monitor RQ = PEC/PNEC?	Yes			
Last date when the the RQ value was last computed/monitored	17-Nov-22	*Enter date*		
What was the RQ value in your effluent water (at the end of the pipe/outlet from your manufacturing site)?	0,8	*Enter RQ between 0 and 10 (eg. 0.7 or 1.5)*	Please share copy of lab test results for API concentration.	
Mixing Zone				
Do you conduct a mass balance/hydrological study on the expected/modeled API discharges for the mixing zone where your treated wastewater is discharged into an external waterbody?	Yes			
What is the frequency of conducting mass balance/hydrological studies for the proposed antibiotic(s)	>1 year			
Do you measure/monitor APIs concentration in the mixing zone where your wastewater is discharged into the environment?	Yes			
What is the frequency of conducting water quality sampling at the mixing zone and testing for the proposed antibiotic(s)	>1 year			
Do you compute and monitor RQ = PEC/PNEC for the water samples taken from the mixing zone?	Yes			
Last date when the the RQ value was last computed/monitored for the samples taken from the mixing zone	17-Nov-22	*Enter date*		
What was the RQ value for the samples taken from the mixing zone?	0,5	*Enter RQ between 0 and 10 (eg. 0.7 or 1.5)*	Please share copy of lab test results for API concentration.	
Off Site Treatment - Combined Effluent Treatment Plant (CETP)				
Do you or the third-party operator measure/monitor APIs concentration in the effluent from the CETP prior to discharge or reuse?	Not Applicable			
What is the frequency of conducting water quality sampling and testing for the proposed antibiotic(s)	Not Applicable			
Do you or the third-party operator compute and monitor RQ = PEC/PNEC?	Not Applicable			
Last date when the the RQ value was last computed/monitored		*Enter date (or leave*		
What was the RQ value in the CETP effluent water (at the end of the pipe/outlet from the CETP)?		*Enter RQ between 0 and 10 (eg. 0.7 or 1.5), leave blank if not applicable*		
Supplier Sites				
Do any of your suppliers measure/monitor APIs concentration in their effluent water (at the end of the pipe/outlet from manufacturing site) prior to discharge or	No			
What is the frequency of conducting water quality sampling and testing for the proposed antibiotic(s) at your supplier sites	>1 year			
Reporting and Data Sharing				
Reporting of environmental performance — Self reporting? TP certification?	3rd Party Certification			
Do you share this data? — Publicly? Within the industry? Shared when asked? Not shared?	Within the industry			

Section 4 - Other Matters		Required Evidence	Supplier Reference Document and Comments
Company size?			
Location of the site (distance from a water body, and is it a pristine water body?) (sensitivity of receiving water body)			
Do you have a programme to take back unused/expired antibiotics for safe and proper disposal?	Yes	Please share copy of relevant documentation	
Has the product been evaluated for its environmental attributes, including persistence, bioaccumulation, toxicity, and environmental risk?	Yes	Please share copy of environmental risk assessment report	
Is the company a member of PSCI or EFPIA or other relevant associations?	Yes	Please share membership certificate/document.	
Does the company follow the PSCI Industry Principles?	Yes	Please share declaration on letterhead.	
Has the PSCI commitment policy been disseminated to suppliers?	No		
Does the manufacturer have a BSI certification of the AMRIA standard?	No		

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