STUDY REPORT

Pharmaceutical Manufacturing Industry – India and AMR: Stakeholder Analysis and Possible Solutions

Image source: www.freepik.com

Report presented at Stakeholder Workshop on One Health Approach to AMR: Environment and Manufacturing Industry, April 2023

Acknowledgement: The market study report was co-authored by Siddhartha Prakash (Shawview Consulting), Nitin Verma and Jahanvi Kulshreshtha (Spans Envirotech), and the authors, extend their heartfelt appreciation to all the participants who took part in the study. The participants' valuable insights and feedback played a pivotal role in providing a comprehensive analysis of the AMR and pharmaceutical industry market trends and dynamics that are presented in the report.

Disclaimer: This publication was funded by the European Union. Its contents are the sole responsibility of the authors and do not necessarily reflect the views of the European Union.

Table of Contents

Abbreviations....iv
Executive Summary 1
Introduction.... 2
Approach and Methodology 4
Theory of Change 4
Methodology 4
Literature Review 4
Stakeholders Consultation Analysis 6
Analysis Summary 7
AMR Awareness Levels.... 14
Actions to Address AMR 17
Recommendations on next steps 24
RAMP Framework 24
AMR Centre of Excellence (CoE).... 25
Annexure A: List of Stakeholders Consulted 27
Annexure B: Stakeholder Interview Questions 29

Abbreviations

AMR	Antimicrobial Resistance
AMRIA	AMR Industry Alliance
BDMAI	Bulk Drug Manufacturing Association of India
BITS	Birla Institute of Technology and Science
CAMF	Common Antibiotics Manufacturing Framework
CEP	Council of EHS Professionals
CETP	Common Effluent treatment Plant
CII	Confederation of Indian Industry
CoE	Centre of Excellence
CPCB	Centre Pollution Control Board
CSE	Centre for Science and Environment
DoP	Department of Pharmaceuticals
EHS	Environment, Health, and Safety
ETP	Effluent Treatment Plant
EU	European Union
FAO	Food and Agriculture Organisation
GDP	Gross Domestic Product
GLG	Global Leaders Group
GMP	Good Manufacturing Practices
HPPCB	Himachal Pradesh Pollution Control Board
ICARS	International Centre for Antimicrobial Resistance Solutions
IDMA	Indian Drugs Manufacturers Association
IPA	Indian Pharmaceutical Association
MoEFCC	Ministry of Environment, Forest and Climate Change
MoU	Memorandum of Understanding
NAP	National Action Plan
NCDC	National Centre for Disease Control
NIPER	National Institutes of Pharmaceutical Education and Research

NGO	Non-Governmental Organisation
NGT	National Green Tribunal
OPPI	Organisation Of Pharmaceutical Producers of India
PNEC	Predicted No-Effect Concentration
PSCI	Pharmaceutical Supply Chain Initiative
RAMP	Responsible Antibiotic Manufacturing Platform
R&D	Research & Development
SAP	State Action Plan (for AMR)
SIWI	Stockholm International Water Institute
TSPCB	Telangana State Pollution Control Board
UNEP	United Nations Environment Program
WOAH	World Organisation for Animal Health
WHO	World Health Organisation
ZLD	Zero Liquid Discharge

Executive Summary

Antimicrobial resistance (AMR) is a major global threat to public health. To address this problem, the One Health approach has been adopted, bringing together stakeholders from multiple sectors. India is a major producer of pharmaceuticals and is known as "the pharmacy of the world." The release of antibiotic residues by the pharmaceutical industry poses an environmental risk of AMR. The Responsible Antibiotics Manufacturing Platform (RAMP) proposed an integrated approach to reduce industry's contribution to AMR in the environment through collaboration between industry, government, and academia. The EU commissioned this study with the aim to assess the insights gained from the RAMP project, gather perspectives from relevant stakeholders regarding the issue of antimicrobial resistance, explore potential solutions, and facilitate collaboration and integration of environmental considerations into the One Health approach.

The study found varying levels of awareness and action among stakeholders regarding AMR from pharmaceutical manufacturing. Most government agencies had medium to high awareness. The awareness and action of industries and associations were mixed, with larger companies claiming significant actions, but smaller manufacturers were less aware. Academic and research institutes were found to have a good understanding, but limited influence, while international agencies were found to have a higher awareness and were taking actions falling in medium to high intensity. Civil society organisations were aware, with efforts focused on awareness and some NGOs measuring antibiotic levels in local rivers. However, there is variability in stakeholder agreement on the intensity of impact compared to other pollution sources. The majority of interviewees had an understanding of the impact of antibiotic manufacturing on AMR, but there is seeming a lack of clarity on required actions. Regular AMR surveillance is either non-existent or still in the early stages of development, while tools, technologies, and solutions are available, capital, and operating costs are seen as significant barriers to change. Whilst it is clear that industry has assumed stewardship in the fight against AMR, some are questioning the need to act when other sectors responsible for AMR are not being targeted, such as human, animal, and hospital sectors.

The research found that whilst different stakeholders are taking action to address the spread of AMR, the implementation of proposed plans is in its early stages. Regular monitoring of antibiotic residues is crucial, and there are available monitoring tools and solutions that require testing, validation, and adaptation to make them effective and accessible. Complex and costly infrastructure development and training are required to monitor antibiotics. The guidelines developed by the Central Pollution Control Board should be applied, and stakeholders need capacity building to conduct regular monitoring. Multi-stakeholder collaboration between government agencies is crucial for effective implementation, and an ecosystem approach could help addressing the challenges for small and medium manufacturers. National and state AMR action plans must prioritise environmental causes of AMR, including antibiotic

manufacturing discharges. The researchers concluded that these actions are critical to address the spread of AMR and protect public health.

The need for collaborative action to reduce environmental pollution from pharmaceutical manufacturing in India to combat AMR is emphasised. The recommendations include exploring multi-stakeholders' collaborations through establishing an AMR Centre of Excellence (CoE) and piloting and refining the RAMP framework in India to develop a universally acceptable framework for monitoring and mitigating the impact of pharmaceutical manufacturing on the spread of AMR. These recommendations can be instrumental in developing effective and sustainable solutions to reduce the impact of AMR in India.

Introduction

Antimicrobial resistance (AMR) is a silent pandemic that is projected to claim 10 million lives by 2030 and lead to a 3.8% reduction in global GDP by 2050 as per the World Health Organisation (WHO). AMR is already a leading cause of death in India due to increasing levels of drug resistance caused by the irrational use of drugs by humans. It is also spreading from poor hospital waste management, water, and sanitation, overuse of antibiotics in poultry feeding and farming practices, as well as from antibiotic manufacturing hotspots.

One Health refers to the collaborative efforts of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals, and our environment. The One Health approach is increasingly popular in the context of growing threats from emerging zoonoses, antimicrobial resistance, and climate change. WHO, the Food and Agriculture Organisation (FAO) of the United Nations, and the World Organisation for Animal Health (WOAH) have been working together to provide strong leadership to endorse the One Health concept and promote interagency and inter-sectoral collaboration.

Cooperation on AMR is also part of the 2025 roadmap for the EU-India Strategic Partnership, and AMR is a topic discussed at the EU-India Joint Working Group on Pharmaceuticals. The EU is funding a four-year regional project on fighting AMR in Asia under the One Health approach, implemented by the Tripartite (WHO, FAO, WOAH). India is one of the nine countries targeted.

In 2022, the Tripartite partnership for One Health formally became the Quadripartite as it signed a Memorandum of Understanding (MoU) with UNEP.

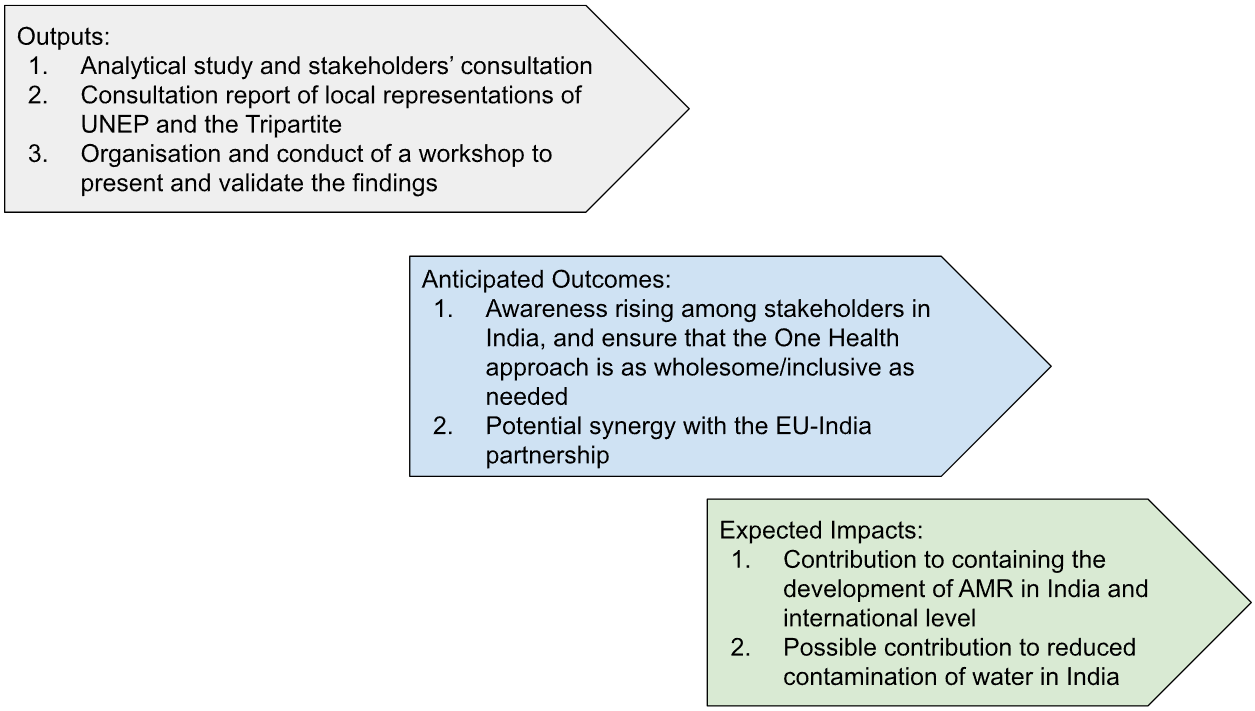
India, hailed as "the pharmacy of the world ", is a major country manufacturing pharmaceutical product: EU imports roughly one-third of its active pharmaceutical ingredients from India, particularly antibiotics. Hence, the AMR risk linked to environmental impact of the manufacturing of antibiotics is of special relevance in the country. Responsible antibiotic manufacturing platform (RAMP) is a consortium of global pioneers led by the Stockholm International Water Institute and Shawview Consulting, with the support of the Swiss Agency for Development Cooperation, AMR Industry Alliance, and its member companies. Over the past few years in India, RAMP attempted to reduce the spread of AMR due to antibiotics in the environment through multi-stakeholder engagement to promote the adoption of sustainable monitoring, manufacturing, and procurement practices in India.

The objective of the present study is to take stock from the learnings from the RAMP project, understand the perception of the issue and possible solutions by relevant stakeholders, and pave the way for possible actions and collaboration, and full integration of the environmental aspects into the One Health approach in cross-sectoral activities.

Approach and Methodology

Theory of Change

The project is expected to contribute to the cause of the spread of AMR in the following ways:



Methodology

1. Desk-based review
2. Stakeholder consultations with key AMR-related stakeholders
3. Identification of global and local monitoring and technology solutions

Literature Review

The team reviewed key global and national reports on AMR including the WHO Global Action Plan on AMR, the UNEP Report on AMR in the Environment[1], the Cost-benefit analysis of industry action by Wellcome Trust[2], Quad strategic framework for collaboration, AMR Industry Alliance Standard, and the RAMP Framework. These reports point towards a growing recognition and global awareness that the discharge of antibiotics and other antimicrobials into the environment is posing serious issues for not only for the environment but also for human health. Several global studies in recent years have highlighted very high concentrations of antimicrobials in rivers and water systems around the world[3].

[1] UNEP Report "Bracing for Superbugs: Strengthening environmental action in the One Health response to antimicrobial resistance" https://www.unep.org/resources/superbugs/environmental-action
[2] https://cms.wellcome.org/sites/default/files/2022-04/understanding-the-antibiotic-manufacturing-ecosystem-2022.pdf
[3] Wilkinson, J. et al. 2022. "Pharmaceutical pollution of the world's rivers", PNAS, Vol. 119 No. 8,

High concentrations of antibiotics in manufacturing hotspots have been detected in India. The emergence of cases across the country, from Baddi in Himachal Pradesh[4], Musi River in Telangana, to Rangpo in Sikkim, is contributing to evidence of these growing concerns. The National Green Tribunal has directed drug manufacturers in these states to reduce the discharge of untreated antibiotics into the environment. This is attracting global attention and calls for action as the G7, G20, and Global Leaders Group on AMR demand action by industry and governments.

These findings are also leading to changes in global procurement[5] practices of European governments[6] and multinationals prioritising environmental and social goals in their procurement of antibiotics. Some countries have revised the selection criteria for the procurement of drugs based on the environmental performance of the supplier. A global shift towards green procurement could have adverse effects on the competitiveness of the Indian pharmaceutical industry.

https://doi.org/10.1073/pnas.2113947119

[4] National Green Tribunal AMR related case details and bench orders can be referred from the website: https://greentribunal.gov.in/caseDetails/DELHI/0701112002812018

[5] WHO's publication from May-2020 of "Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance"

[6] Swedish National Agency for Public Procurement has published environmental criteria for procurement of medicinal products including antibiotics, reference: The National Agency for Public Procurement.

Our literature review included country-level studies on national and state-level AMR action plans, the Indian Council for Medical Research Report on AMR in the environment, the RAMP white paper on sustainable antibiotic manufacturing in India, Non-Governmental Organisations (NGOs) reports[7] on antibiotic manufacturing residues in select Indian states, and draft government guidelines for monitoring antibiotic residues in India.

The Ministry of Health and Family Welfare, Government of India, has spearheaded the efforts to develop the National Action Plan on AMR. The Central Pollution Control Board (CPCB, Ministry of Environment, Forest and Climate Change) has been active in developing environmental standards and protocols for antibiotic monitoring in water bodies and proposed draft antibiotic discharge and monitoring standards and guidelines in January 2020[8].

Stakeholders Consultation Analysis

The team prepared a list of 40 experts to be interviewed from industry, NGOs, academia, government, and donors, along with a set of questions to assess levels of awareness and understanding of AMR in the environment, stakeholder involvement, and influence as well as global and national approaches to monitor and reduce the contribution of antibiotic manufacturing to the spread of AMR in the environment. Details of the stakeholders and questionnaire can be found in the annexes to this report.

The team reached out to all stakeholders targeted for the study. However, only about 15 experts largely from industry, academia, NGOs, and international donors participated in the detailed interview (as shown in the table below). We have divided our findings into two broad categories: AMR awareness levels; and actions required by different stakeholders.

Table: Summary of Stakeholder Consultations

	Detailed Interview	**Short-Interview**
Tripartite & International Development Agencies	WHO FAO ICARS WOAH Wellcome Trust SIWI[9] / RAMP	2030 Water Resources Group (the World Bank)

[7] Scoping Report on Antimicrobial Resistance in India, Centre for Disease Dynamics and Economic Policy, November 2017.
Rivers across the world have high levels of antibiotics, Down to Earth, 20 May 2019.
[8] Relevant NGT Case Details including the moniotrin guidelines, petetion, and court orders can be founder at https://greentribunal.gov.in/caseDetails/DELHI/0701102008582020.
[9] Stockholm International Water Institute (SIWI)

Government of India	ICMR (NICED)	HPPCB TSPCB DoP Dr. Renu Swarup (former Secretary, DBT)
Industry	AMR Industry Alliance OPPI IPA Dr. Reddy's Laboratories Aurobindo Pharma Centrient Pharmaceuticals	CII, PSCI
Academia	IIT Bombay	University of Hyderabad
Civil Society	Veterans Forum, Council of EHS Professionals	

Analysis Summary

The stakeholder analysis was done based on the relative level of awareness and actions currently being taken to reduce the impacts of antibiotics manufacturing on the spread of AMR. The analysis has been pictorially summarised in the following three charts.

1. Stakeholder Mapping based on level of awareness, action on the ground, and level of influence on the antibiotics manufacturing sector. (Figure 1)
2. Stakeholder Mapping on a Wardley Map to show the interplays between the different stakeholders and their relative level of maturity with respect to awareness of the problem (Wardley Map 1: Assessment of Awareness of the Role of Pharma Manufacturing on the spread of AMR)
3. Stakeholder Mapping on a Wardley Map to show the interplays between the different stakeholders and their relative level of maturity with respect to actions being taken presently to reduce the impact of manufacturing on the spread of AMR (Wardley Map 2: Assessment of Actions to Stop the Spread of AMR)

Guide on how to read the stakeholder map

- The map represents various stakeholders/stakeholder groups on a coordinate plane in the form of coloured bubbles.
- The X-axis shows the level of awareness of the stakeholders. Awareness increases from low to high as we go from left to right on the map.
- The Y-axis shows the level/intensity of actions from low to high as we go from bottom to top on the map.
- The size of the bubble represents the influence of the stakeholders on reducing AMR from manufacturing.

Guide on how to read the Wardley Maps

A Wardley map is a visual representation of the various elements of the AMR ecosystem, and their relationships to each other and to external factors. It is used to help understand and analyse the landscape of the problem statement, and positioning of the different stakeholders, and to identify opportunities for action and improvement.

Here are some steps to help read a Wardley map:

- Understand the axes: A Wardley map consists of two axes, the x-axis, and the y-axis. The x-axis represents the level of evolution or maturity of a component, from genesis (new and uncertain) to commodity (well-established and predictable). The y-axis represents the value chain or the flow of value from the user/customer to the supplier/producer.
    - X-Axis in Wardley Map 1 is divided into four sections comprising “Not well understood”, “Initial Level of Understanding”, “Well Understood” and “Universal Truth”. This is to help showcase the relative positioning of different stakeholders with respect to their level of awareness as well as the agreement of the stakeholders on the problem statement.
    - Y-Axis in Wardley Map 1 spans from Visible to Invisible (top to bottom), representing the relative positioning of the different elements of the ecosystem being evaluated.
    - X-Axis in Wardley Map 2 is divided into four sections comprising “Ideation”, “Development”, “Refinement”, and “Scale”. This is to help demonstrate the level of maturity of the actions that are currently being taken to reduce the impact of manufacturing on the spread of AMR.
    - Y-Axis in Wardley Map 2 spans from Visible to Invisible (top to bottom), representing the relative positioning of the different elements of the ecosystem being evaluated.
- Identify the components: The components on a Wardley map are represented by nodes or boxes. Each node represents a specific stakeholder or action with respect to AMR. The nodes are positioned on the map according to their position on the x and y axes.
- Analyse the relationships: The relationships between the stakeholders and actions are represented by lines. These lines indicate the interactions, the dependencies between different stakeholders and actions, and the relative positioning of the stakeholders with respect to the evolution of the problem statement (i.e., AMR from manufacturing). The lines may also represent feedback loops, market forces, or other external factors that affect the evolution of the stakeholders or actions.
- Identify patterns: Wardley maps help depict patterns or clusters of stakeholders and actions that share similar characteristics. These patterns can help identify areas of opportunity or risk and can help inform strategic decisions.
- Interpreting the map: It is important to interpret the map in the context of the core concept being studied, i.e. “Spread of AMR because of Pharmaceutical Manufacturing” which is being analysed. This visual representation helps us better consider the implications of the role of different stakeholders, their actions, efforts and also for identifying areas for improvement and supportive actions.

Key observations from the stakeholder mapping (Figure 1)

- The majority of stakeholders consulted were found to have a good understanding of the problem related to spread of AMR from pharmaceutical manufacturing.

- The relative awareness level of most government agencies ranges from medium to high, but actions taken by them mostly fall in low to medium intensity. Government agencies, especially the Ministry of Environment, Forest and Climate Change and Pollution Control Boards, were deemed to have high influence, hence, any action from these agencies could have significant impacts on the reduction of spread of AMR.
- Academic and research institutes in India were found to have a good understanding of the problem and are carrying out some activities (mostly around studies of pollution levels and research and development of new ways of monitoring antibiotics and drug resistant microorganisms) but their reach and influence was generally found to be limited to academic circles.
- International agencies were deemed to be aware of the situation and also taking actions that range from medium to high intensity. However, relative to government agencies, the influence of international agencies is considered to be less impactful.
- Awareness levels in the industries and industrial associations were found to be quite dispersed. This is indicative of the diverse nature of industries - small scale to large scale as well as international vs local industries. In general, the awareness and action of this stakeholder group was found to be mixed. The researchers found that larger pharma companies and industrial groups claim to be taking significant actions to reduce the impact of their operations on spread of AMR. For the authors, this is likely due to the stewardship the AMR Industry Alliance and its members have demonstrated over the last few years. However, the smaller manufacturers were considered to be less aware of the impact of antibiotic discharge in the environment, especially in the veterinary sector.
- Most civil society organisations surveyed were found to be aware of the AMR challenge. The bulk of their efforts researchers found, were focused on awareness-raising. Some NGOs have attempted to measure levels of antibiotics in local rivers. In one case, their actions have resulted in a legal case in the National Green Tribunal.

Key observations from, and explanations to the Wardley Map 1

- The overall awareness of the impact of manufacturing on the spread of AMR was deemed to be well understood among the stakeholders working on these issues. However, a number of environmental, health and safety professionals working in antibiotic manufacturing plants and the general public remain unaware of AMR It is anticipated that with continued efforts would increase awareness among all key stakeholders. There seems to be variability in agreement of the different stakeholders on the relative intensity of the impact in comparison to other sources of pollution e.g., hospital waste and sewage.
- The level of awareness and in general the agreement on the problem statement seems to have matured over time. According to the authors, this is most likely due to greater awareness and more data that is available to link the impact of pharmaceutical manufacturing wastes on the spread of AMR and pressure from global procurers and international agencies.
- The general level of awareness and agreement at the international development agencies and large multinational pharma companies is more mature compared to the level of awareness among government, local industry and civil society organisations.
- The level of awareness within government agencies was estimated to vary, especially across the different levels of the government. Regulators such as the Ministry of Environment, Forest and Climate Change and the pollution control boards were deemed to be well aware of the challenges

and to have been working on finding solutions to reduce the AMR.

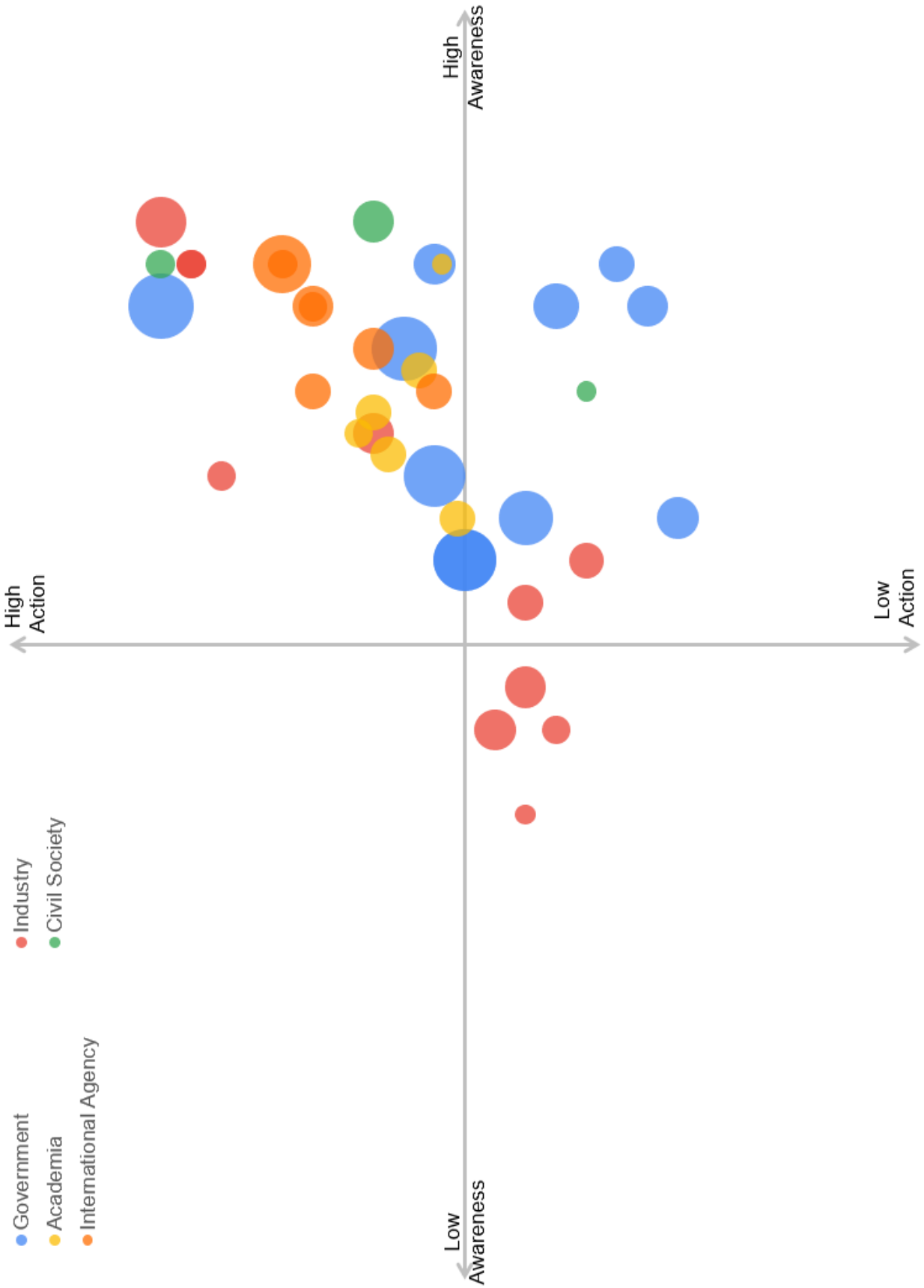
- The overall awareness of civil society at large was found to be in the initial stages and a highly variable level of awareness among different people and organisations belonging to this sector. There seems to be a need to put in additional efforts and resources to increase the overall awareness among civil society which can help in having greater and more widespread positive impact in the long run.

Key observations from, and explanations to the Wardley Map 2

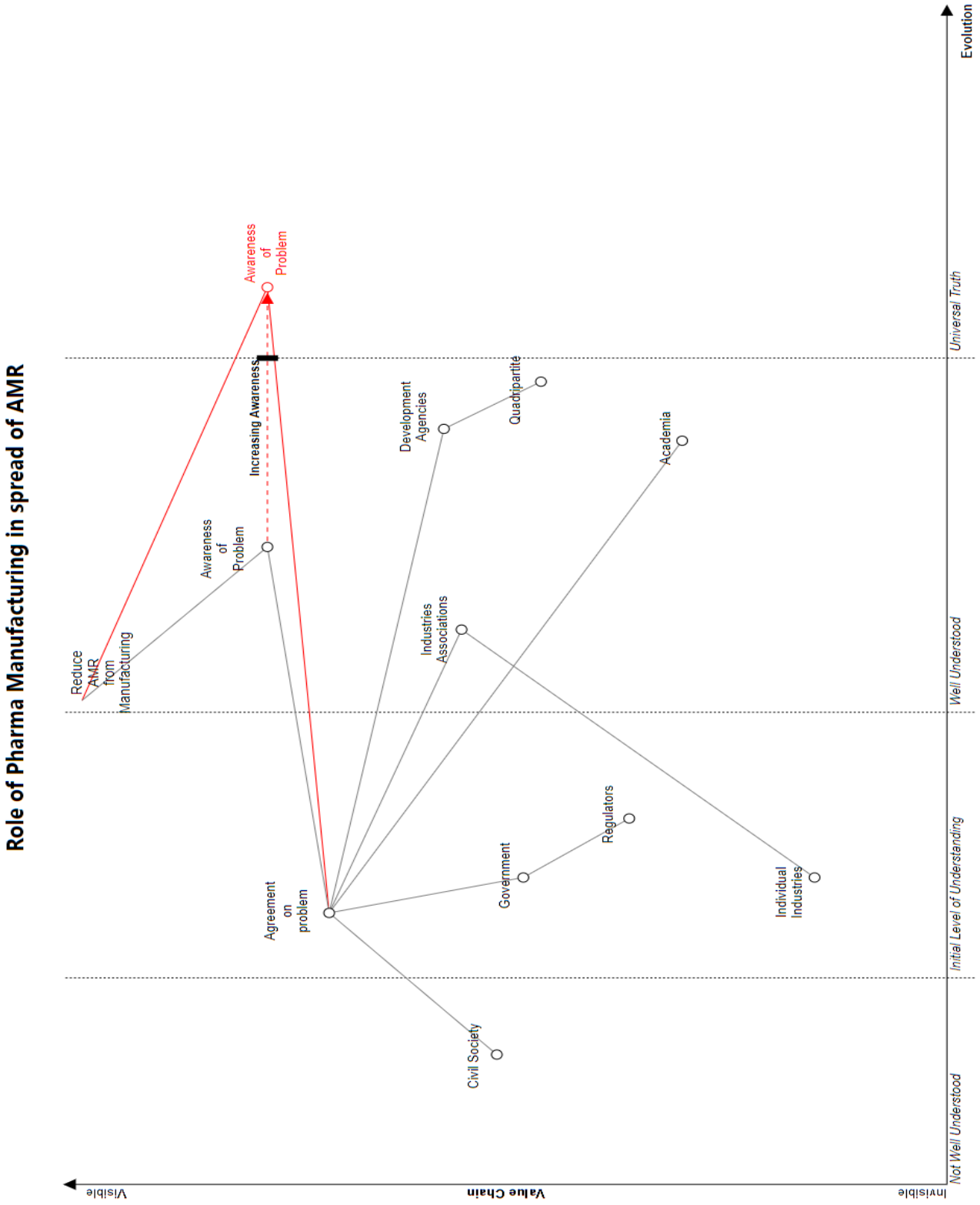
- This Wardley Map aims to represent the relative scale of actions and activities undertaken by the different stakeholders.
- Indian regulators have been working on developing the world's first regulation for monitoring and limiting the concentration of antibiotics in the waste streams from pharmaceutical manufacturing facilities. However, the proposed regulations and guidelines are still in a nascent / ideation stage and have reportedly also faced resistance from industry.
- Whilst there seems to be some initial efforts of coordinated action, it is deemed as being in its initial stages of development. For example, the Government of India, regulators, and industry have often been found to refer to the global best practices recommended by the global AMR Industry Alliance which has developed responsible business practices such as the Common Antibiotics Manufacturing Framework guidelines[10].
- There are global and local efforts on new research and development, however, there seems to be a need for more coordinated action and refinement of the R&D efforts to work on key and specific problem statements. For example, the Birla Institute of Technology and Science (Hyderabad) partnered with CPCB to develop new river water quality monitoring techniques. Such collaboration and coordinated efforts are expected to create immense value overtime.
- Industry stewardship has been a key enabler for wider awareness of the challenge and investments into development of new techniques and solutions for reducing the impact of manufacturing on spread of AMR. However, based on stakeholder interviews, the level of awareness as well as action on the ground was highly variable at the individual industry level. The links between industry associations and capacity building of individual industries appears to be an area where more coordinated efforts are required for more widespread action.
- While development agencies have been proactively advocating action against spread of AMR, their role especially with respect to pharmaceutical manufacturing was found to be limited and in early stages.

[10] AMR Industry Alliance CAMF and Manufacturing Standard https://www.amrindustryalliance.org/wp-content/uploads/2018/02/AMR_Industry_Alliance_Manufacturing_F ramework.pdf and https://www.amrindustryalliance.org/antibiotic-manufacturing-standard/

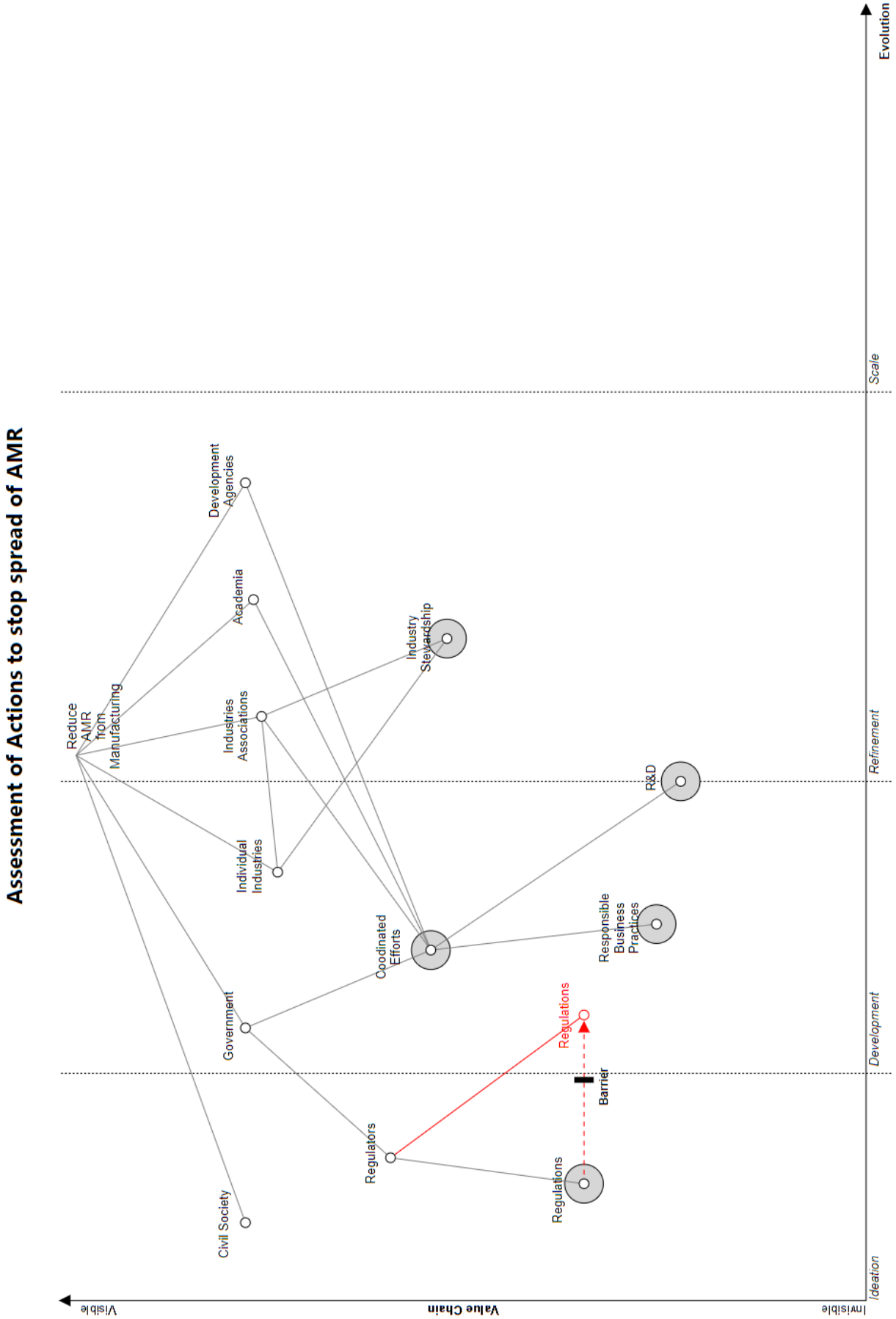
Figure 1: Stakeholder Awareness and Action Mapping



Wardley Map 1: Assessment of Awareness of the Role of Pharma Manufacturing on the spread of AMR



Wardley Map 2: Assessment of Actions to Stop the Spread of AMR



AMR Awareness Levels

Based on the consultations, following is the summary of the awareness levels among the stakeholders in the Indian ecosystem, as established by the research team.

1. Most interviewees were aware of the impact of antibiotic manufacturing on AMR.
2. There is a lack of clarity on regulations and actions needed.
3. Regular surveillance is missing or in nascent stages.
4. Tools, technologies, and solutions are available and not considered to be a limiting factor.
5. However, capital and operating costs are considered to be major perceived barriers to change.
6. Industry needs to assume stewardship for the fight against AMR.
7. Companies claim that other sectors responsible for AMR are not being actively targeted (e.g., human, animal, and hospital).

The following sections provide detailed insights into these findings.

The Contribution of Antibiotic Manufacturing to AMR

Antibiotics released in the environment through various sources including manufacturing is a potential cause of AMR. Awareness about the environmental and manufacturing dimensions of AMR is increasing, however continues to vary among stakeholders, especially among key regulatory implementation agencies, antibiotic manufacturers and relevant government agencies. India has a significant number of antibiotic manufacturing industries and thus a high potential for relatively high concentrations of antibiotics in manufacturing clusters. The environmental risk is also compounded by hospital waste and uses in agriculture or aquaculture. The impact of antibiotics in the environment on creation of AMR is still subject to scientific investigations. AMR transmission is complex as cycles for breakdown vary for different antibiotics and its study requires an interdisciplinary approach.

In India, active pharmaceutical ingredients used to manufacture antibiotics are mainly being produced in certain pharmaceutical clusters in five states in the country, increasing the risk of contribution to the development and spread of AMR from these manufacturing hotspots. Some of the manufacturing units and common effluent treatment plants (CETPs) are inefficient in treating the wastewater and contribute to contaminating local water bodies, leading to development of drug-resistant microbes. Small and medium-sized companies are dependent on these government-run CETPs which may not entirely be sensitive towards the AMR issue.

Other contributing factors to AMR include irresponsible usage of antimicrobials, deficient hygiene and infection control, and poor containment of resistant infections. It is important to consider all drivers of AMR and the links between factors related human health, animal husbandry, agriculture and the environment, in order to take actions in a systematic and coordinated way, i.e. via the “One Health’’ approach to AMR. The environmental aspect needs to contemplate, beside other sources of contamination, the manufacturing component of AMR, both globally and in national AMR action plans.

The Risks of Taking No Action

Inadequately controlled environmental emissions contribute to AMR. If left unchecked, it could develop and spread more rapidly, increasing the public health risk. If companies are unable to meet standards required by purchasers, it will also create an economic risk. Assessing the cost of action versus the cost of inaction is important, in order to build consensus.

Studies by local NGOs[11] indicate the current situation around AMR is serious and actions are needed since several companies are allegedly discharging their untreated waste into the environment despite having effluent treatment plants (ETP) and zero-liquid discharge (ZLD) systems in place.

Industry Response and Actions

Some industry associations like the Pharmaceutical Supply Chain Initiative (PSCI) have undertaken several initiatives to promote awareness about AMR in the environment and ways to reduce antibiotic residues. These include organising sensitisation workshops with local companies and state governments. The AMR Industry Alliance (AMRIA), representing the global pharmaceutical industry, has developed guidelines to monitor antibiotics and a standard to promote good manufacturing practices. Over 20 AMRIA manufacturing members based in US, Europe, and Asia have committed to meeting these standards to meet their predicted no-effect concentration (PNEC) value. They assess their own and direct suppliers' manufacturing practices which involve site auditing, mass balance evaluation, sampling, and analysis with timely corrective action plans and management systems. This sometimes requires additions or changes in their manufacturing process including a reduction in water consumption and the use of additional treatment technology.

In the absence of a global/statutory standard, voluntary standards and initiatives are applied by the members of the organisations, but they lack scale of application. For instance, only 30% of global antibiotic manufacturers are members of AMRIA. Moreover, the steps taken may be insufficient to address AMR, and have the risk of lock-in effects for moving on to alternative standards in the absence of regulatory standards.

Indian drug manufacturers are on various levels of evolution in their sustainability journeys. Subsidiaries of global multinational companies and their suppliers are beginning to monitor antibiotic residues, along with some large Indian antibiotic manufacturers. But many generic companies remain unaware of the AMR issues and the risks associated with the discharge of untreated antibiotic residues into the environment. A number of small companies lack the knowledge, resources, and solutions to address these challenges.

Small-scale industries are allowed to send primary treated wastewater to CETPs. Large-scale industries are required to treat the wastewater until tertiary treatment before sending it to CETPs. In one State, the absence of CETPs running tertiary treatment 24/7 results in high antibiotic concentrations in wastewaters and higher concentrations in the surrounding environment due to sewage and other discharges, while in another State, some CETPs segregate industrial from domestic sewage streams, and apply different treatment methods for each stream. The underlying observation is that the implementation, and engineering solutions adopted for treatment at the CETPs vary significantly across the country.

The Central Government is mandating a zero-liquid discharge (ZLD) policy to the pharmaceutical manufacturers. As per the policy, no solid or liquid waste should be discharged from the factory, it may be

[11] Link to NGT Case Details: https://greentribunal.gov.in/caseDetails/DELHI/0701102008582020

re-used or sold to cement factories. Though the policy was not mandated for addressing AMR, companies have been found to claim that the risk of release of antibiotics in the environment is minimal with ZLD and the procedure has become more efficient and less costly over the past years. However, there are no scientific studies demonstrating the effectiveness of the implementation of the ZLD policy[12] and its impacts across the different states in India.

At the manufacturing plant level, segregation of the manufacturing waste stream from other process streams and domestic waste is required to make the ZLD process cost-effective, with high AMR risk streams of wastewater requiring a higher degree of treatment. Some companies have developed internal procedures and guidelines to destroy the activity of antibiotics and bring them below predicted no-effect concentration (PNEC) levels. However, conventional treatment techniques cannot be used to degrade antibiotics.

Available Monitoring Technologies and Solutions

Water treatment should be checked to confirm it has achieved the PNEC values for antibiotics. Most local companies have stressed the need for access to better monitoring technologies and solutions. While some new monitoring solutions exist, the credibility and reliability of these technologies is not confirmed as they are not accredited. The complex science behind global technologies is not always easy to understand, adapt and replicate in local settings.

It is difficult to monitor PNEC values, particularly in generics that have multi-product interferences. In many cases, due to the lack of technology, mass balance is used for measuring residual antibiotics in untreated wastewater, although this is a hypothetical exercise.

Some argue whilst the current approach of following PNEC values to prevent selective concentrations is right, its implementation in the mixing zone (point in the receiving water body where the wastewater discharged from the manufacturing facility mixes with the waterbody) is not practical because of the significant time and space between emission points and mixing zones. There is a need to verify how the discharge parameters are being met, and what happens to the eject from the Reverse Osmosis system, solid waste, crystallised salts, concentrated brine, etc.

Data can be generated using proper analytical methods, instruments, and technology. This needs to be validated with actual water sampling, monitoring, and analysis, which is a complex and costly process. At present, there are no benchmark standards to verify if the collected data correlate to the environmental risks except for a few antibiotics produced exclusively by a few manufacturing units. Although reliable data can be generated by measuring, it is very costly and technical know-how for measuring low concentrations is scarce and not standardised, (to take into account interference of organic matter during measurements). Hence a number of global companies are sending their waste samples from India to Europe for laboratory testing.

There is tremendous scope for innovation, research, and action in developing technologies for easier and cheaper monitoring. Traditional methods of monitoring, such as the use of liquid chromatography-mass spectrometry technologies, are very costly and will not be sustainable for widespread use by manufacturers and regulators. Some research focuses on developing low-cost sensor technologies to monitor antibiotic

residues from factories and CETPs, which could make monitoring easier.

Monitoring and Data Gaps

Public data is mostly gathered and reported by academics and NGOs conducting field studies. The challenge found by the authors is that most companies do not undertake regular monitoring as there are no regulations requiring them to do so. The Government of India has requested antibiotic manufacturers to share their data publicly, but many companies are reluctant to share their data or allow third-party factory audits. Moreover, current data focus on modelled emission data and ZLD as a proxy for good practice, which is costly and has infrastructure limitations (labs) and cannot be verified. Existing data are insufficient to point to a specific effluent stream or concentration peak which allows for ambiguity and makes accountability difficult. As a result, there are few direct studies that correlate antibiotic residues from manufacturing to local levels of drug resistance in the environment.

Changes in Global Procurement Practices

A number of international pharmaceutical companies and European drug procurement agencies are beginning to change their procurement practices towards green procurement. There are some procurement pilots looking at how to bring environmental and responsible manufacturing measures into their procurement criteria for medicines. For example, the Swedish National Agency for Public Procurement has issued sustainability criteria for procurement of pharmaceuticals. In Norway, under the new system, "environmentally friendly production will be weighted by 30 percent as allocation criteria"[13]. Going forward, global procurers may bar or disengage with suppliers that fail to demonstrate that they follow good environmental practices. Procurers use specialised agencies to check the claims made by manufacturers. The volume of purchases that follow the sustainability criteria is not significant yet but is growing with more and more countries considering it (e.g. Denmark, Finland, Germany, Iceland, Norway, Sweden, Portugal and UK). Hence India would gain from being proactive and leading the debate, shaping the outcome and required actions.

Actions to Address AMR

The following actions are those either implemented or recommended in the Indian ecosystem by the interviewed stakeholders:

1. A range of monitoring tools, technologies, and solutions are available that vary from costly liquid chromatography-mass spectrometry to low-cost sensor technologies. These need to be tested, validated, and adapted for monitoring antibiotics presence in the environment.
2. Monitoring antibiotics is a complex process and requires costly laboratory infrastructure development and the training of professionals as well as regulators.
3. Application of guidelines developed by CPCB are critical to streamlining regular monitoring.
4. Capacity building of stakeholders across different levels is needed to undertake regular monitoring of antibiotic residues.
5. Regulations need to be accompanied by multi-stakeholder collaboration between different government agencies including departments of engineering, environment, and health.

[13] https://sykehusinnkjop.no/nyheter/new-environmental-criteria-for-the-procurement-of-pharmaceuticals .

6. Implementation challenges for small and medium manufacturers need to be addressed through an ecosystem approach that extends from the factory to the common effluent treatment plant.
7. National and state AMR action plans need to prioritise a focus on the environmental causes of AMR including antibiotic manufacturing discharges.

The following section provides detailed insights into these findings.

Further Actions Required by Industry

There is only a portion of manufacturers (mostly large multinationals and their supplier base) that are taking actions to monitor their discharges for antibiotic residues and treat their wastewater up to tertiary level and practice Zero Liquid Discharge (ZLD). The current approach is believed to be insufficient because not all companies and sites are acting on the problem.

It is important to monitor and verify the claims made by industries, including what happens to the by-products of treatment - reverse osmosis reject, solid waste, crystallised salts, and concentrated brine.

There are gaps in the knowledge related to AMR and its consequences and the industry has not been sensitised and made aware of them. This knowledge gap and lack of monitoring and treatment infrastructure also extend to the government-run CETPs that often receive primary-treated water from small manufacturers and tertiary-treated wastewater from large-scale manufacturers. With added sewage and other discharges, CETP wastewaters can have higher (and more complex) antibiotic concentrations and consequently higher concentrations in the surrounding environment.

Different Approaches for Measuring and Reducing Antibiotic Residues

Awareness about the approaches to reduce and monitor antibiotic discharges into the environment is mixed among the stakeholders. While some were aware of methods like predictive environmental concentration (PEC), antibiotic resistance genes, and PNEC for monitoring, other stakeholders, mostly of non-technical backgrounds were unfamiliar with the details. There is a general consensus on the need for clear, verifiable, and accessible new, cost-effective approaches and for spreading awareness and education about existing techniques and their methodologies through seminars, publications, and interactions.

Systematic environmental monitoring of both antibiotics and resistance genes is required. Monitoring is a significant challenge where new technologies are needed to detect antibiotics in the environment and also quantify resistant bacteria and antibiotic resistant genes.

Role of Regulations and Guidelines for Monitoring Antibiotics in the Environment

Monitoring is a complex process that involves different procedures for measuring different antibiotics and needs to be performed, interpreted, validated, and verified by methods and actors accepted by all stakeholders.

There is an agreement on the need for regulations and guidelines for responsible antibiotic manufacturing among the interviewees. The guidelines must be science-driven, and equitable, and must not disrupt the fragile antibiotic supply chain. Guidelines would help ensure safe discharge levels, simplify processes, and converge focus on advocacy and action amongst the stakeholders.

A robust environmental management system with regulatory requirements would help manufacturers to demonstrate their actions and their results. This may include quantification of antibiotics in waste streams through mass balance and its verification by sampling waste streams meeting PNEC by independent third-party evaluation.

However, there are challenges to implementing these guidelines, such as determining the owner of the guidelines, validating standards, and creating a business case for adoption with adequate resources for regulatory roll-out and monitoring. Additionally, it would be most beneficial for the guidelines to evolve as per the ongoing updates based on validated scientific data.

There were suggestions to develop GMP-like standards owned by an international body like WHO. However, there are concerns that GMP-like standards would give rise to confusion and conflicts in the jurisdictions that the guidelines-framing body and local statutory bodies may have over Indian manufacturing clusters. One suggestion is to adopt country-by-country regulation that is science-driven, risk-based, carefully planned, and implemented.

The implementation and control of regulations are important, and capacity building across the ecosystem is necessary to ensure compliance. India has a high volume of antibiotic manufacturing and would greatly benefit from being a pioneer in rolling out regulations. Some stakeholders suggest developing formal regulations to regulate antibiotic release in the environment.

Currently, in the absence of statutory regulations, standards adopted by the AMR Industry Alliance members are suggested by some as a good standard to follow. Regulators may also acknowledge these standards and adopt them as a basis for developing new and more advanced standards. Also, it is important to consider all contributing sources of AMR-causing contaminants, including manufacturing, hospitals, animal husbandry, sewage, and food while developing these standards.

Cost of Implementation and Incentives Required

Reducing the impact of manufacturing on AMR is essential for public health, but it comes at a cost. The cost has been found to vary depending on the antibiotic being manufactured, the company's business model, the size of the manufacturing unit, and the quantity of water used, making it difficult to establish industry requirements and the average cost involved. While all API manufacturers in India are statutorily required to conform to ZLD norms, the high cost of treatment technologies are deemed to be an impediment to compliance, and a general lack of transparency in the manufacturing and treatment process hampers verification.

The expenses for actions required for curbing the spread of AMR are majorly in the treatment of wastewater discharges from manufacturing and monitoring and analysis of the discharge samples. As the methodologies and lab infrastructure required for monitoring and analysis of wastewater samples are not easily available in India. Samples collected in India are often sent to laboratories in Europe for testing and analysis which leads to high transfer costs and thus to the high overall cost of analysis. Findings of a report by the Wellcome Trust estimate that profit margins for manufacturers, after adopting periodic analysis and treatment of antibiotics, may drop from 4% to 12% depending on the intensity of standards applied. While larger manufacturers with higher profit margins may consider such investments, generic and small-scale manufacturers with smaller markets and profits may be more impacted by the drop in margins.

It can be argued that it is a joint responsibility to act on reducing the impact of manufacturing on AMR as it affects public health. While some stakeholders advocated sharing of costs among them, some quoted the 'polluter pays'' principle. Others suggest that cost should not hinder progress toward AMR compliance and that the first movers will benefit the most in the future. There is no one-size-fits-all approach to help reduce the impact of manufacturing on AMR. There could be various ways - positive reinforcement as well as penalties that would motivate the industry to move towards compliance and responsible manufacturing. The global procurers could add procurement terms and conditions specific to the environmental effects of antibiotic manufacturing, rewarding the industry investing in responsible manufacturing of antibiotics.

Following are some of the ways suggested by different stakeholders:

1. Awareness and mass education among all stakeholders to understand the impact of AMR and actions required to curb it. Regulatory bodies and other government agencies will benefit from capacity-building on the environmental aspect of AMR for policy advocacy.
2. Regulations should be applied in a supply chain-sensitive way, based on scientific evidence, rolled out in a phased manner with short-, medium- and long-term strategies for pan-India compliance. Guidance and handholding may be required in the initial phase to motivate early adoption and regular compliance with the goal to bring everyone to a certain level.
3. Optimise the cost of treatment and ZLD by segregating high-concentration streams from other streams before treatment, developing new and cheaper technologies for monitoring and treatment, developing centralised systems for small-scale manufacturers in a cluster.
4. Government incentives such as environmental grants from industrial policies, longer duration consents, discounts in consent fees, recognition, and reward for consistently meeting the bar, relaxation in taxes, and fast-track approval of Environmental Impact Assessments may help.
5. Capacity building, handholding, and technical expert knowledge can be made available to small companies through an alliance of manufacturers, procurers, and government agencies.
6. Technology transfers through international cooperation for a global public good and applying procurement conditions in a supply chain-sensitive way.
7. Heavy penalties for non-compliance and reducing years of consent can act as a 'stick' to the manufacturers.
8. Sharing of cost among the stakeholders – manufacturers, procurers, and government.

Monitoring Action and Implementation Challenges

Given the multi-sectoral attributes of the spread and impact of AMR, actions are to be taken by several agencies and collaboration among them is crucial. Suggestions made to monitor effective action and its impact on AMR include self-assessment, certification, and verification of compliance claims either by independent experts or external private or public bodies. There is a compelling case for public-private sector partnerships and coordination and collaboration of multiple stakeholders (involving decision-makers, technical specialists, and treatment process experts) to enforce compliance, and map actions on the ground among the manufacturers.

One could argue that making data available is a mixed public and industrial responsibility of manufacturers

just like the data of general effluent monitoring and should be rewarded. Data may best be generated not only from larger manufacturers but also from smaller manufacturers and CETPs to comprehend the gaps and the risks. There were suggestions for the creation of a national task force to map pharmaceutical industries and identify hotspots of prevalent antibiotic residues in the environment which can focus on prioritising action and monitoring performance. The collected data could be stored on a dashboard on an online platform for verification and can be used for certification and setting accountability by government agencies in case of any violations or non-compliance. In contrast, some stakeholders suggest certification of compliance with periodic monitoring and analysis and the involvement of regulators, customers/procurers, and government agencies from time to time instead of real-time monitoring.

Several stakeholders emphasised prioritising the framing of the regulations and global standards which in turn will drive the industries to adopt responsible practices to address AMR. Regulations or national environmental standards may also be included in Good Manufacturing Practices Compendiums for wider acceptance.

The research found that improvements on the existing approaches may be needed to standardise them and optimise their costs for wider acceptability in the industry. Direct reading-type instruments are recommended to simplify the monitoring process. The gap in the availability of dedicated infrastructure like monitoring devices, low-cost treatment technologies, analytical instruments, and testing laboratories needs to be addressed. Pilot setups should be made available to familiarise manufacturers with the process. Proper protocols are necessary to avoid interferences while measuring. Methods would need to be standardised against ‘‘gold standard’’ methods. Validated methods of monitoring and analysis should be developed simultaneously and in consensus. These methods must be scientifically validated, scalable, and upgradable to cater to future needs. Data collected through one method would also need to be verified with others for coherence.

There is a need to involve academia and researchers in the process to keep upgrading the technologies and evolving the standards and guidelines. This will establish a cycle of data that can be provided by the manufacturers and government agencies based on which researchers and academia can come up with new technologies and guidelines to be enforced by regulators and complied with by manufacturers.

To ensure that regulatory standards are met, certificates are sanctioned, and procurement is carried out effectively it is important to invest in infrastructure, human resources, and the development of technical skills.

As AMR is a comparatively new topic for most stakeholders, several gaps were identified in the skills and abilities required for impactful action against the spread of AMR. Training and workshops may be required to improve the skills of personnel working not only in the laboratories and manufacturing units but capabilities of different regulators that need to be enhanced. These workshops may also lead to the establishment of multi-stakeholder platforms to coordinate and develop approaches to address the problem, increase awareness, share technical knowledge, and build consensus amongst stakeholders. Stakeholders would require capacity-building for regular testing and monitoring. Organisations such as PSCI, CPCBs, other government authorities, and civil society organisations could be approached to help in educating the stakeholders and civil society.

Targeting the Small-Scale Manufacturers

Small manufacturers of human and animal antibiotics form a major portion of the drug manufacturing community and collectively produce large quantities of low-cost generic medicines. They usually lack the resources to implement sustainable manufacturing and discharge treatment practices, as often these manufacturers have thin margins. Additional responsible manufacturing and AMR compliance creates a question of affordability and survival of business rather than just a drop in the revenues which in turn may impact the supply of crucial medicines.

The Government of India could benefit most from supporting a positive approach to bring all manufacturers (small, medium, and large scale) into the discussion rather than the alternative of making AMR compliance an area of competition. Extending measures taken by some companies to all or more companies are deemed likely be the most impactful activity.

Following are some of the suggestions for targeting the inclusion of small manufacturing units in curbing AMR:

1. Regulatory authorities and the government could bring small companies together for efficient transfer of knowledge and data sharing, giving them a voice in the discussions about AMR and inculcating synergy among them.
2. Small companies should understand the cost of compliance and the support they need instead of dismissing it on the basis of cost.
3. Incentives like tax breaks, subsidies, fast-track processes, low-interest loans, rewards and certification of compliance etc., could be provided to encourage sustainable manufacturing.
4. Larger companies that source products from contract manufacturers could help their contractors comply with sustainable manufacturing practices. There should be cost sharing between contractors and buyers
5. Small industries could use shared centralised resources for the treatment of their discharges and laboratory for analysis with the support of the local or state governments.
6. Government could also help in sharing technologies and help to scale the technologies with respect to cost and efficiency for small manufacturers.
7. CETPs catering to pharma hubs and clusters of small manufacturers could be strengthened to meet regular water discharge standards rather than them doing it individually for each unit.
8. Small manufacturers could build relationships with pharmaceutical industry organisations for capacity building.

Environment and AMR Action Plans

The environmental component to address the issue of antibiotic contamination in the environment in the current National Action Plan for AMR (2019), or the State Action Plans (SAP) released so far, was found to be limited. During discussions with various stakeholders, several steps were suggested by them to develop a systematic approach for integrating sustainable antibiotic manufacturing into the design of the environmental components of country AMR action plans which are discussed below.

There is a need to spread information about the topic of AMR as there is limited data available for policy advocacy in the government agencies which will lead to the development of regulations and guidelines for the manufacturers and other stakeholders.

There is also a need for capacity building for technical requirements and infrastructure to run pilot tests in CETPs or manufacturing unit ETPs to demonstrate the use of recommended technologies and open discussions on the topic and develop solutions through consensus.

Data collected from such pilot tests, SAP's implementation experience, and research in the field of AMR can be used to further develop the manufacturing and environmental components of the Action Plans for better implementation. Following successful pilot studies, medium-sized businesses, and generic manufacturers should be brought in for discussion and sharing technologies tested by researchers with them.

It is important to understand that pilot projects, draft regulations, and draft action plans may not be the most advanced versions, but there is an urgent need to start implementing its recommendations due to the seriousness of the consequences of AMR.

Interaction of public health departments at the local, state, and national levels and businesses will also play an important role in the wider acceptance and concrete action on the ground. An independent body of stakeholders could be formed to ensure consensus and quick and smooth decisions and action monitoring. Such a group will also be helpful in deciding the responsibilities, providing technical assistance by pulling experts from various fields, and resource allocation to ensure coordination and proper representation of all and develop possible solutions in advance.

NGOs and other private organisations could help integrating sustainable antibiotic manufacturing into the design of the environmental components of AMR action plans. Independent studies done by these groups can be collectively very significant for stakeholder mapping and data collection and collaboration. Once the national and state AMR action plans are developed, they should include the allocation of financial, infrastructural, and technical resources to build the capacity of local companies and state regulators to implement the environmental components of the state AMR Action Plans. This will require funding for laboratories and low costs technologies dedicated to monitoring and testing antibiotic residues.

Role of Stakeholders in Addressing the Challenge

Stakeholders could create an ecosystem that is supportive and demanding for responsible manufacturing. Coherence is desirable between the supply and demand side, policy and market instruments, as well as accountability. The entire supply chain is made up of the contributors – purchaser/buyer, regulator (environmental and pharmaceutical regulators, GMP), and manufacturers (especially API manufacturing). In India. Governments (Central and State) have the biggest role.

All stakeholders – regulators, academia, civil society organisations, and international bodies - have a role to play and could create a body acceptable to all parties to plan and coordinate progress. For example, the Global Leaders Group on AMR can drive the AMR agenda globally, promote R&D, and monitor the global AMR burden and response. International development partners and UN agencies can support innovative companies to develop new antibiotics and provide technical assistance to help governments and local companies to adopt sustainable antibiotic manufacturing practices. Governments play an important role in

developing policies and creating financial and regulatory incentives that will drive responsible manufacturing for minimising the AMR risk and ensuring that the industry remain competitive. The Ministry of Health and Family Welfare and the Ministry of Environment, Forest and Climate Change have a critical role to play to regulate the manufacturing of antibiotics.

It would be important that involvement and coordination between multiple stakeholders follow the One Health Approach and work simultaneously on several fronts. One of the major challenges in multi-sectoral problems is resource allocation and coordination among different agencies which is lacking in the current action plans. A consensus and synergy are required among the stakeholders, where the guidance and support of international bodies/forums such as WHO, UNEP, FAO, WOAH and G20 will act as leverage for ensuring coherence between countries and stakeholders. They can help, for instance, in developing coordinated training modules for sustainable procurement criteria for procurement agencies, and good practices for producers to meet and demonstrate that these criteria are met.

NGOs and academics can develop innovative monitoring tools and conduct field investigations and report on gaps and actions required. For example, the Council of Environment, Health, and Safety (EHS) Professionals is a global platform of about 15,000 members that connects people of all pharma industries and can be used to start spreading awareness about the AMR issue across the industry and further cascade it to the management level.

Industry can play an important role in changing business practices by adopting and investing in sustainable antibiotic manufacturing practices to reduce AMR and remain globally competitive. There is a lack of synergy among these different stakeholders leading to confusion and people working in silos. A harmonised approach is required to set the course for coordinated multi-stakeholder collaboration on AMR.

Recommendations on Next Steps

The growing awareness of AMR in India is conducive to implementing action to reduce the impact of environmental pollution from pharmaceutical manufacturing. Considering this, there are a few recommendations that can be considered to facilitate the reduction of AMR spread.

Firstly, exploring multi-stakeholder collaborations is important to encourage collective action. One way to achieve this is by establishing and successfully running an AMR Centre of Excellence (CoE) that brings together representatives from the government, industry, civil society, and academia to work together towards a common goal of reducing the impact of pharmaceutical manufacturing on the environment and spread of AMR. Such a centre could serve as a hub for sharing knowledge and best practices, and for developing and implementing solutions for addressing the spread of AMR.

Secondly, it is recommended to pilot test and refine the proposed RAMP framework in India. This would enable stakeholders to identify any potential gaps or limitations in the framework and refine it to make it more universally acceptable for monitoring and mitigating the impact of pharmaceutical manufacturing on the spread of AMR. A well-developed and refined framework would be instrumental in guiding the development of effective and sustainable solutions to address the problem of AMR spread in India. The AMR CoE could help validate the framework for the Indian context and help further refine the framework for wider adoption.

RAMP Framework

The suggested standard by the AMR Industry Alliance and the British Standards Institute, as well as the

monitoring guidelines and draft regulations by CPCB, are crucial initial steps towards reducing the impact of pharmaceutical manufacturing on the spread of AMR. These voluntary initiatives should be recognised for their leadership in establishing international standards for responsible antibiotic manufacturing. However, due to significant gaps in science, methodology, and implementation scale, there is disagreement over whether these standards address all the issues in antibiotic pollution. As a result, some parts of the pharmaceutical industry have introduced manufacturing standards without a consensus among stakeholders on the best practices for antibiotic manufacturing. Insufficient cooperation among stakeholders and lack of progress in addressing antibiotic pollution may lead to standards that do not meet the needs of other stakeholders and the community, or adequately address environmental issues in the long-term.

To help address this issue, RAMP has developed an independent framework that systematises different compliance control options and suggests criteria applicable as an interface between the demand side and the supplier. The RAMP framework is designed for use by various groups, including procurers, regulators, local and national governments, pharmaceutical companies, and industry groups. It provides impartial and harmonised criteria that go beyond the current voluntary commitments of the industry. For example, the framework looks at different treatment technologies (ZLD vs non-ZLD, or ETP vs CETP) as well as different points of reuse (horticulture vs utilities) in order to look at the various practices commonly followed in the industry today and help form a common baseline for the assessment of the environmental footprint of a pharmaceutical manufacturing plant and its potential impact on the spread of AMR. Other stakeholders, such as non-governmental organisations, academics, investors, and antibiotic manufacturers, can also benefit from the framework's enabling conditions, although they are not directly involved in industry implementation.

The RAMP Framework focuses on criteria within the immediate control of the manufacturer or subcontractor, such as wastewater treatment facilities. It aims to be universally applicable and contribute to transparency and accountability between relevant parties. The purpose of this framework is to drive consensus and collaboration on the best practices for antibiotic manufacturing standards among all stakeholders.

Ultimately, the RAMP framework provides a set of criteria and tools that promote responsible manufacturing while addressing the risks of AMR. Its objective is to minimise the exposure of environmental bacteria to antibiotics from manufacturing waste streams, considering various perspectives from stakeholders and scientific options. The framework seeks to harmonise different approaches used by stakeholders, including voluntary industry standards and scientific publications, among others.

AMR Centre of Excellence (CoE)

In order to address the impacts of antibiotics manufacturing on the environment, the RAMP partners are developing an AMR Centre of Excellence (CoE) in India to advance the One Health approach. The Indian Government (through Department of Pharmaceuticals and Government of Telangana) are co-financing and developing the CoE in partnership with Dr. Reddy’s Laboratories, Indian Institute of Technology Bombay, Council of EHS Professionals, Shawview Consulting, and Commonwealth Scientific and Industrial Research Organisation (CSIRO, Australia). The CoE will bring together the global expertise of industry, and the scientific capabilities of national research institutes and regulators under a public-private partnership to develop the capacity of industry, and government stakeholders to monitor and adopt sustainable manufacturing practices.

AMR COE Priority Areas

The key objective of the CoE is to equip the pharmaceutical industry for sustainable manufacturing to combat AMR through:

1. Providing a multi-stakeholder platform for spreading awareness and advancing collaborative action in the fight against AMR.
2. Addressing capacity building and training needs of industry and government.
3. Supporting the upgradation of infrastructure for testing and treating antibiotics.

Once established, the CoE would provide the following core services:

1. Academic training to industry, regulators, and procurement agencies on various topics including AMR in the environment, testing for antibiotics in water samples, treatment solutions, waste management practices, etc.
2. Laboratory partnerships for testing and verification of the latest monitoring technologies and solutions. CoE will partner with analytical laboratories for testing and verification using a variety of approaches (Mass Balance, Innovative Sensor Technologies, High Performance Liquid Chromatography, Gas Chromatography/Mass Spectrometry, use of Big Data, artificial intelligence/machine learning technologies, etc). These will be available to both industry and government agencies like the state pollution control boards.
3. Technology Testbed for testing and validation of new treatment technologies (such as Advanced Oxidation, filtration, reverse osmosis, evaporation, new monitoring sensors, energy-efficient equipment, technologies, etc).
4. Policy research and advocacy to support the development of national and state-level AMR Action Plans, development of national guidelines for monitoring antibiotics, and additional capacity-building needs of stakeholders.

The CoE will adopt best practices and global standards to develop the ecosystem for sustainable antibiotic manufacturing. This would involve working at the factory level to advise EHS and sustainability professionals at manufacturing sites about AMR, monitoring methodologies, and industry good practices. These would include guiding local antibiotic manufacturers on the use of sensor technologies and mass balance calculations. Moving from the factory to the cluster level, guidelines will be developed for the creation of AMR-compliant CETPs across India. The lessons learned from these operations will serve to guide the co-creation of the environmental component of the state AMR action plans. Various training courses (short-term, long-term, and certification) will be conducted to train/upskill the manpower for monitoring and mitigation of antibiotic discharge in the environment.

Annexure A: List of Stakeholders Consulted

S.No.	Agency
Government of India	
1.	Ministry of Environment, Forest and Climate Change (MoEFCC)
2.	Central Pollution Control Board (CPCB)
3.	State Pollution Control Board - Himachal Pradesh[14]
4.	State Pollution Control Board - Telangana[12]
5.	Department of Pharmaceuticals
6.	Department of Biotechnology
7.	Ministry of Health and Family Welfare
8.	National Centre for Disease Control
9.	Indian Council for Medical Research (ICMR)
10.	National Green Tribunal (NGT)
Industry Associations and Key Industries	
11.	Indian Drugs Manufacturers Association (IDMA)
12.	Indian Pharmaceutical Association (IPA)
13.	Bulk Drug Manufacturing Association of India (BDMAI)
14.	AMR Industry Alliance (AMRIA)
15.	Pharmaceutical Export Promotion Council of India (PharmExcil)
16.	Organisation of Pharmaceutical Producers of India (OPPI)
17.	Confederation of Indian Industries (CII)
18.	Dr. Reddy's Laboratories
19.	Aurobindo Pharma

[14] *Selected because of the high concentration of pharmaceutical manufacturing with a representation of small, medium, and large-scale industries. Further, there is documented history of antibiotic pollution-related challenges.

S.No.	Agency
20.	Centrient Pharmaceuticals
21.	Covalent Laboratories
Academic and Research Institutes	
22.	BITS Hyderabad
23.	NIPER Hyderabad
24.	IIT Hyderabad
25.	IIT Chennai
26.	IIT Bombay
27.	University of Hyderabad
Civil Society Organisations	
28.	Centre for Science and Environment (CSE)
29.	Veterans Forum
30.	Council of EHS Professionals (CEP)
International agencies/experts	
31.	World Organisation for Animal Health (WOAH) [formerly OIE]
32.	World Health Organisation (WHO)
33.	Food and Agriculture Organisation (FAO)
34.	Center for Disease Dynamics, Economics & Policy (CDDEP)
35.	Wellcome Trust
36.	UK Research and Innovation (UKRI)
37.	United Nations Environment Program (UNEP)
38.	Dr. Renu Swarup (former Secretary, DBT)
39.	CK Mishra (former MoEFCC/MoHFW)

Annexure B: Stakeholder Interview Questions

Awareness-assessment of the situation

1. What is your opinion on the impact of antibiotic manufacturing on the development of AMR?
2. Do you see any risks of inaction towards addressing the impact of manufacturing on AMR?
3. Do you think that responsible antibiotics manufacturing is needed? And if so, why?
4. Who are the most important contributors to the debate on the impact of manufacturing on AMR, at the national and international levels? What do you think their roles are and should be?
5. What steps are companies taking to reduce their antibiotic emissions in the environment?
6. Do you think there is sufficient reliable data available on the current levels of residual antibiotic discharges from manufacturing? And if not, how can the data be generated?
7. Do you think there are technologies and solutions available for regular monitoring and verification of the claims of responsible manufacturing made by manufacturers?
8. Are you aware of the steps global procurers have taken to ensure responsible manufacturing of antibiotics and how this could impact India's drug exports?

Action by the stakeholders

1. Do you think the industry's current approach is sufficient to curb the spread of AMR from manufacturing? If not, why not? What do you think can be done to improve the industry's approach?
2. Are you familiar with the different approaches to reduce and monitor antibiotic discharges into the environment such as PEC and alternative approaches? Do you see a need for further spreading knowledge about those approaches or a need for developing more techniques and methods?
3. Do you agree that there is a need to develop and adopt guidelines for responsible antibiotics manufacturing? What are the benefits and challenges of developing these?
4. Should regulations be developed, and, if so, how?
5. Would global standards be needed, and, if so, why?
6. Do you have any idea about the costs of action for reducing the impact of manufacturing on AMR? What incentives are required to motivate the domestic industry to become AMR compliant?
7. How would you see the best way to monitor effective action and its impact: industry sharing data (which ones)? External control (by whom, how: statutory body, external auditors / procurers)?
8. What is the capacity-building needs of industry and regulators for effective monitoring of antibiotic residues - laboratory infrastructure, technical skills, human resources, etc?
9. How does one target the small manufacturers of human and animal antibiotics that lack the resources to implement sustainable manufacturing practices?

Disclaimer: This publication was funded by the European Union. Its contents are the sole responsibility of the authors and do not necessarily reflect the views of the European Union.