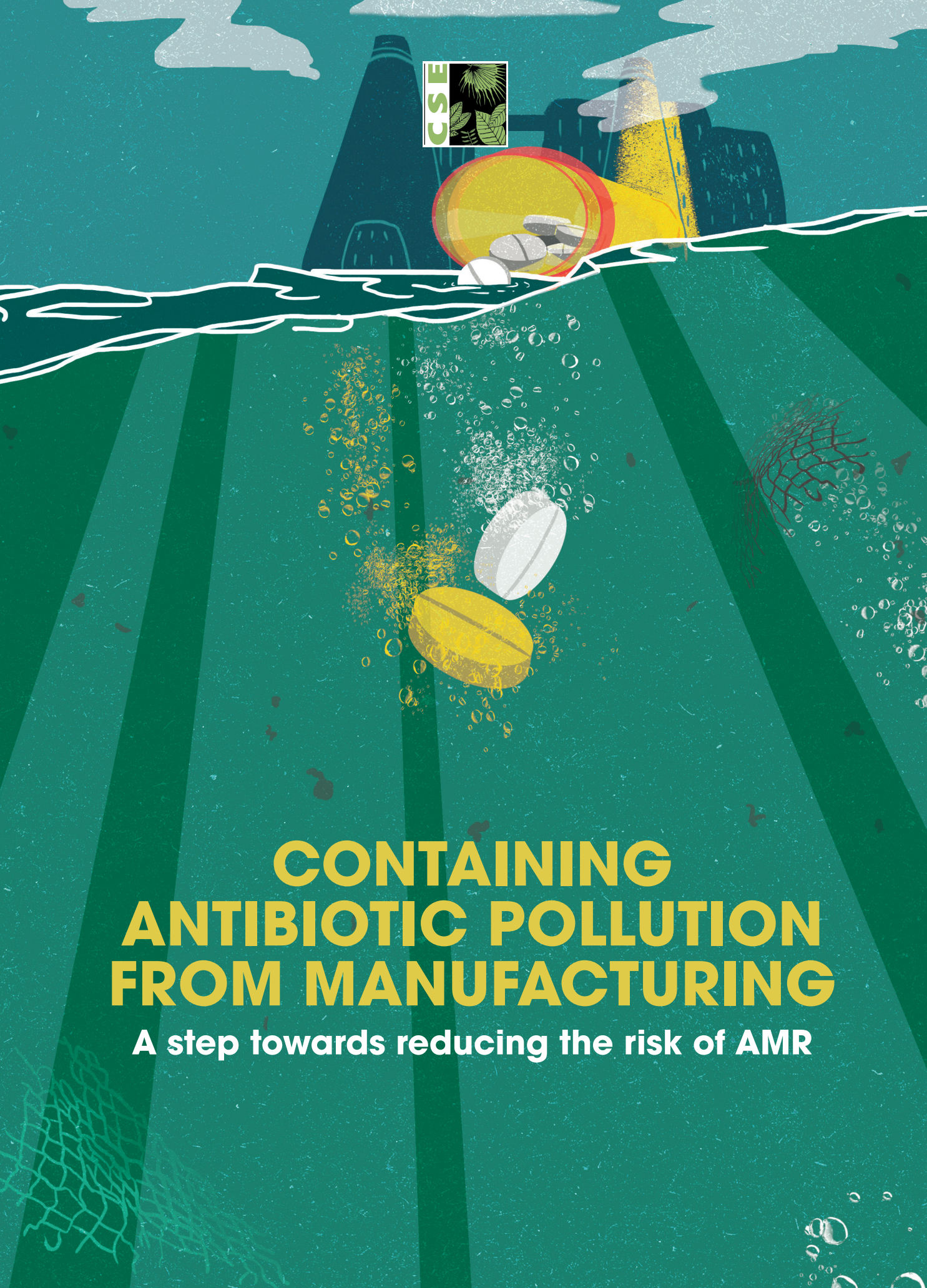

CONTAINING ANTIBIOTIC POLLUTION FROM MANUFACTURING

A step towards reducing the risk of AMR

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Contents

Executive summary

The presence of antibiotics in the environment is known to be a driver of antimicrobial resistance (AMR)—antibiotic resistance in particular—and poses a global public health crisis. Discharge from manufacturing companies containing antibiotics is considered as one of the potential sources that increases the risk of the development and spread of antibiotic resistance in the environment. The presence of antibiotics could be due to inadequate process control measures while manufacturing or due to a lack of or inadequate wastewater treatment before release.

Globally, there is emerging evidence of the presence of antibiotics, resistance-causing genetic material and resistant bacteria in the wastewater released from antibiotic manufacturing or from wastewater treatment plants that receive antibiotic manufacturing discharge or effluents. Antibiotics have also been found downstream of manufacturing sites such as in rivers. Certain gaps have also been identified. These include, for example, the impact of such discharge on human health. But a consensus has been emerging among global stakeholders that the current level of understanding and evidence provide sufficient impetus for action against antibiotic pollution from manufacturing and further evidence being generated can continue to inform action.

Global developments

The global concern to address the issue of antibiotic pollution from manufacturing discharge is gradually building up in multiple ways. The Global Leaders Group (GLG) on AMR in 2022, made a 'call to action' to stakeholders, including countries, pharmaceutical industries and the scientific community to improve the management of discharges into the environment that may contribute to the emergence and spread of AMR.

In 2020, the World Health Organization (WHO) adopted the environmental aspects of manufacturing into the good manufacturing practices (GMP). It made recommendations and laid out expectations from manufacturers related to risk assessment, environmental protection, effluent treatment, and adequate documentation for different aspects of waste management.

In 2021, the Group of Seven (G7) nations recognized the need for an agreement on the standards for antibiotics in manufacturing discharge and mainstreaming them, purchasing/reimbursing antibiotics manufactured as per these standards, accelerating the adoption of changes in WHO GMP with regard to waste and wastewater from antimicrobial production, and using manufacturing and environmental standard related guiding principles for more sustainable antimicrobial drug development.

The European Union (EU) also highlighted the concern that emissions from some antimicrobial manufacturing plants in third countries which could be supplying to the EU, could be contributing to the development and spread of AMR at a global level. It considers the possibility of using procurement policy to encourage greener pharmaceutical design and manufacturing, and encourage action in third countries. It called upon public buyers to design smart and innovative procurement procedures, by improving aspects such as 'green production'. Sweden for example, plans to procure and incentivize environmentally sustainable antibiotics through a national initiative on 'environmental premium', a national level sustainability criteria for medicines, and an antibiotic procurement criterion in Region Stockholm.

In response to the AMR crisis, over 100 members of the global biopharmaceutical industry came together to form the AMR Industry Alliance in 2017. The Alliance has been working across multiple aspects. It has developed Predicted No-Effect Concentration (PNEC) targets for antibiotic residues in pharmaceutical effluents to guide environmental risk assessments. The PNEC targets can be used to derive discharge targets. It is expected that members of the Alliance will work towards achieving these target values at the receiving water body. It has also released the 'Antibiotic Manufacturing Standard' which provides guidance to manufacturers in the global antibiotic supply chain to manufacture antibiotics responsibly. The Alliance, along with the British Standard Institution (BSI), has launched a certification scheme that will enable antibiotic manufacturers to demonstrate through independent third-party evaluation, that waste streams containing antibiotic active pharmaceutical ingredient (API) and drug products are appropriately controlled during manufacturing by pharmaceutical companies. However, the AMR Industry Alliance progress reports suggest that adoption of the Common Antibiotic Manufacturing Framework (CAMF) and achieving the PNEC targets is less successful at supplier sites as compared to member sites.

Indian scenario

India as part of the global antibiotic supply chain

India is an important part of the global antibiotic supply chain. The overall antibiotic import in 2021–22, including both active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs), was 32,567 metric tonne (MT) and the overall antibiotic export was 1,15,911 MT. Almost all of the imports were antibiotic APIs (about 98 per cent) and FPPs were a major share of the exports (about 72 per cent of exports).

The total quantity of antibiotic APIs imported was 31,786 MT and about 80 per cent of it was from China. Penicillins and sulphonamides were the top two classes imported. The total amount of antibiotic APIs exported out of India in the same year was 32,619.4 MT. Sulphonamides and penicillins were also the largest exported antibiotic API categories (85

per cent of total antibiotic API export). Region-wise, about 22.5 per cent of penicillin and sulphonamide was exported to Asian countries, 42.6 per cent to Africa and 17.5 per cent to Latin America.

The total quantity of FPPs imported was only 780.9 MT with cephalosporins being the largest imported class. The total quantity of antibiotic FPPs exported out of India was 83,291 MT. There were 49 different types of antibiotics exported, with those belonging to classes of penicillins and cephalosporins contributing about 45 per cent of this export. These are largely exported to countries like United States of America (USA), France, Ethiopia, Iraq and South Africa. Of the key antibiotic FPPs exported, 44 per cent were exported to African countries, 29.1 per cent to Asia, 5.5 per cent to Latin America, 8.8 per cent to North America and 11.4 per cent to Europe.

India's pharmaceutical manufacturing industry

India's pharmaceutical manufacturing industry ranked third globally in production during the year 2022–23. The domestic anti-infective segment was about 14 per cent of the market share in 2020 and includes antibiotics, antifungals, antiprotozoals, anthelminthics, antivirals, and antimycobacterials. Antibiotic manufacturing in India is largely spread across 25 locations/hubs across nine states which are Punjab, Himachal Pradesh, Telangana, Andhra Pradesh, Karnataka, Gujarat, Maharashtra, Goa and Sikkim. There could be several hundred antibiotic manufacturing companies in these hubs. The exact number is not known.

The 'Schedule M' of the Drugs and Cosmetics Rules 1945 provides the GMP requirements to be fulfilled in order to get license for manufacturing of sale or distribution of drugs. Regarding waste management, the GMP requirements suggest compliance with the local and/or national laws related to waste management.

As per the pollution index (PI) score-based categorization, the API/bulk pharmaceutical industry are categorized under the 'red' category while the formulation industry comes under 'orange' category. A higher value of PI denotes an increasing degree of pollution load from the industrial sector. An industrial sector with a PI score of 60 and above is categorized as red, while those with PI score of 41–59 is categorized as orange. The standards for waste from pharmaceutical industry includes compulsory parameters like biological oxygen demand (BOD), chemical oxygen demand (COD), total suspended solids (TSS), pH etc., and additional parameters like phosphates, sulphides, zinc, copper, arsenic, mercury etc. But like other countries of the world, it does not contain limits for antibiotic residues.

In 2020, India's Ministry of Environment, Forest and Climate Change (MoEFCC) had proposed limiting values for antibiotic residues in the treated effluent of bulk drug, formulation industry and CETP as part of the draft standards put

out for comments. It listed 121 antibiotics. But finally, the standards notified by the MoEFCC in August 2021 were without the limits for antibiotic residues.

In April 2022, the National Green Tribunal (NGT) in response to a petition, ruled that the draft notification containing limits for antibiotic residues, should be strictly followed by all concerned. Subsequently, the case moved to the Supreme Court of India, which has currently imposed a stay on operation of the NGT verdict where the case is being heard.

Responding to an interim order by the NGT, the Central Pollution Control Board (CPCB) had developed guidelines on monitoring mechanism for API residues and released it in January, 2022. It outlines detailed requirements for analysis of antibiotic residues, frequency of monitoring as well as duties of state pollution control boards (SPCBs) and pollution control committees (PCC). The guideline also provides recommendations for the mitigation of AMR in the environment, and for reducing the input of antibiotics into the environment.

With respect to waste management practices followed by the antibiotic manufacturing industry, large-scale companies often claim to focus on process control measures (e.g., mass balance, equipment cleaning, spill control), in addition to resource-intensive waste management technologies/approaches such as zero liquid discharge (ZLD) technology. Small/medium-scale companies usually send the primary treated waste to the common effluent treatment plants (CETP), while some of them also opt for deactivation (using strong alkali like sodium hydroxide) along with primary treatment before sending wastewater to the CETP. These wastewater treatment approaches are adopted depending on the cost of the technology and feasibility of implementation. In addition, there are also some advanced technologies of wastewater treatments which have been shown in published literature to be quite efficient in degrading antibiotics present in pharmaceutical wastewater samples.

Common Effluent Treatment Plants

Out of the 25 antibiotic manufacturing hubs across nine states, 16 hubs across six states have a total of 35 CETPs of varying capacities, ranging from 0.5–55 million litres per day (MLD). Out of these 35, only four have wastewater recovery systems. While many hubs have multiple CETPs, Sikkim, Punjab and Goa, with five hubs in total, do not have any CETPs in these hubs. Two hubs in Himachal Pradesh, one in Maharashtra and one in Karnataka also do not have CETPs.

The CETPs are also categorized under 'red' category, but they come under special category projects as these are part of pollution control facilities. For a CETP, the categorization also depends upon the category of member industries being served. As per the CPCB, CETPs are required to carry out online continuous effluent quality monitoring. The Environment

(Protection) Amendment Rules, 2015 provides quality standards for the treated effluent leaving the CETP and disposed into three different areas, which are inland surface water, land for irrigation and into the sea. These include general parameters like BOD, COD, TSS, fixed dissolved solids (FDS), pH, and specific parameters like phosphates, sulphides, zinc, copper, arsenic, mercury etc. The State Pollution Control Board (SPCB) prescribes the inlet quality standards as per design of the CETP and local needs and conditions. Not surprisingly, as of now there are no standards for residual antibiotics in treated effluents released from CETPs. The limiting values for antibiotic residues as per the 2020 draft MoEFCC standards were however meant to be applicable at the final outlet of manufacturing unit's ETP and CETPs connected to it.

Based on the understanding developed from select two CETPs—Baddi CETP, located in Baddi-Barotiwala-Nalagarh (BBN) area of Himachal Pradesh, which is a formulation producing hub and Jeedimetla Effluent Treatment Limited (JETL), located in Hyderabad in the state of Telangana, which largely caters API producers—it was apparent that both have different approaches of wastewater management. While Baddi CETP segregates wastewater based on the type of industry and treats it separately, JETL distributes waste stream irrespective of industry into high and low totally dissolved solids (TDS) and treats it accordingly. The JETL has modified its infrastructure to include multiple effect evaporators, agitated thin film dryers and reverse osmosis, such that it can operate as a ZLD facility and treat high and low TDS effluents. Baddi CETP, on the other hand, does not have such facilities, but uses a cost-effective approach of treating the pharmaceutical effluent twice. The cost involved and its calculation is also different in both cases.

Way forward

The report clearly suggests that:

- The consensus to act on manufacturing discharge is growing globally.
- The AMR Industry Alliance response is in the right direction but lacks scale and implementation.
- There are huge expectations from the Indian pharmaceutical industry.
- There are no standards to directly address antibiotics in manufacturing discharge.
- The antibiotic limits proposed in the draft Indian standard are yet to be notified.
- Pharmaceutical companies adopt a varying set of waste management approaches based on several factors.
- Most CETPs in antibiotic hubs rely on conventional treatment approaches.
- Waste management approaches are best when adopted based on specific factors of a company/CETP.

It is also clear that India and the Indian pharmaceutical industry should act because:

- Action on antibiotics in manufacturing discharge can be very effective in containing the spread of resistance.
- Effective action is linked to several challenges, which need to be systematically addressed.

- India's pharmaceutical industry stands to gain in the long-term, only if it initiates in a timely manner and supports effective action.
- India will be hugely benefitted from effective action. This can be an opportunity to invest in preventing a potential future health and economic crisis.

What we need to do

National and state government ministries/departments, regulatory agencies, scientific and academic institutes should:

1. Invest in creating awareness and building the capacity of stakeholders involved.
2. Develop data to support policy formulation, implementation and monitoring.
3. Formulate and implement a long-term research agenda.
4. Carry out regular surveillance and monitoring of manufacturing units and CETPs.
5. Strengthen laboratory capacity to support surveillance efforts.
6. Notify legal limits for antibiotics in discharge from manufacturing units and CETPs.
7. Upgrade and enable capacity and capability of CETPs to address antibiotics.
8. Support small-and medium-scale companies in managing antibiotic discharges.

The antibiotic manufacturing (API/FPP) industry in India should:

9. Focus and invest on process control measures, which are like prevention.
10. Build in-house capacity and upgrade waste treatment systems aimed at eliminating antibiotics in manufacturing discharge.
11. Support surveillance, policy-making and sharing of data.

Introduction: Antimicrobial resistance and antibiotic pollution from manufacturing

Antibiotic resistance—a silent pandemic with huge impact

The ability of bacteria and other microbes to resist the drugs used to inhibit or kill them is known as antimicrobial resistance (AMR).[1] It is the microbe, not the person, animal or plant being treated, that becomes resistant to antimicrobials. Resistant microbes can transfer between humans, animals, plants, food and the environment. When bacteria becomes resistant to antibiotics, it is called antibiotic resistance. Antibiotic resistance, unlike Covid-19, is considered a silent pandemic, which is a huge threat to humanity.

With growing antibiotic resistance, antibiotics are increasingly becoming ineffective in treating infections, including those that were otherwise common and easily treatable. It is leading to deaths, morbidity, high treatment cost and increased hospital stays. The new antibiotic development pipeline is thin and fragile, and the problem can worsen, if the

DEVELOPMENT AND SPREAD OF ANTIBIOTIC RESISTANCE[2,3,4]

Although the selection for antibiotic resistance in bacteria occurs naturally over time, it can accelerate when bacteria is exposed to antibiotics. Therefore, antibiotic misuse and overuse in human health, animal health, food-animal and crop production are known to drive resistance. The presence of antibiotics exerts a greater selection pressure on bacteria, causing susceptible populations to die and the resistant ones to survive. This can happen in the gut of animals and humans as well as in soil and water bodies, when antibiotics come in contact with bacteria. Therefore, waste from food-animal production farms (e.g., poultry, dairy, fish and pig farms), factories (e.g. antibiotic manufacturing, meat processing units, slaughter houses), and healthcare settings (e.g. human and veterinary care) increases the risk of the development and spread of antibiotic resistance.

At the molecular level, antibiotic resistance can be intrinsic or acquired. Intrinsic resistance is naturally occurring resistance wherein bacteria can involve mechanisms that limit the antibiotic uptake or pump out or deactivate the antibiotic such as by producing an enzyme, modifying the target site of antibiotic action, developing new processes that avoid using the antibiotic target. Acquired antibiotic resistance can occur by transfer of genetic material from one bacterium to another through the horizontal gene transfer mechanisms. The bacteria can acquire new genetic material from the environment (known as transformation), by direct transfer of genetic material from one bacterium to another through a protein tube (known as conjugation), or by bacteriophages (viruses that infect bacteria) picking up genetic material in the process of infection and passing it onto the bacteria (known as transduction). Resistance to one antibiotic can lead to other antibiotics when co-selection of multiple antibiotic resistance genes happens due to their co-location in the same genetic element. Biocides, herbicides and some heavy metals can create a co-selective pressure. Cross-selection of resistance occurs when a single molecular mechanism can confer resistance to multiple antibiotics (e.g., efflux pumps in bacteria).

antibiotic pipeline continues to remain less promising *(see Box: Development and spread of antibiotic resistance)*.

In 2019, about five million deaths worldwide were estimated to be associated with antibiotic resistance.[5] About 1.3 million deaths were directly attributed to it. AMR, can also impact food security, livelihood, universal health coverage and the attainment of several sustainable development goals. In 2017, World Bank estimated that the global increase in healthcare costs are expected to reach up to USD 1.2 trillion per year by 2050 in a high AMR impact scenario.[6] In a similar situation, the world will lose 3.8 per cent of its annual GDP by 2050 and there could be up to 10 million deaths annually, with the most deaths happening in Asia and Africa.[7]

Antibiotic manufacturing discharge—a potential source of antibiotic resistance

Due to inadequate process control measures while manufacturing or inadequate wastewater treatment before release, antibiotic manufacturing discharge can contain antibiotics at concentrations that can create pressure to select for resistance in the bacteria present in the receiving environment (e.g. water).[8] Such discharge therefore, is considered a source that can increase the risk of the development and the spread of antibiotic resistance in the environment. This can reach humans through routes such as the food chain. In addition to passing resistance traits to the next generation of bacteria, these resistant bacteria can also transfer resistance conferring genes to other bacteria in the vicinity through horizontal gene transfer mechanisms and make them resistant.

The global scientific community continues to develop evidence related to the presence of antibiotics, resistance causing genetic material and resistant bacteria in the wastewater released from antibiotic manufacturing or those released from wastewater treatment plants receiving antibiotic manufacturing discharge. Antibiotics have also been found downstream of manufacturing sites such as in rivers. Over the last decade, there are studies from countries like China, Vietnam, Pakistan, Nigeria, Korea, Taiwan, Croatia, Switzerland and India that have highlighted the presence of one or more of these resistance determinants in pharmaceutical manufacturing wastewater or sediments *(see Annexure 1 and Annexure 2)*. The concept of predicted no effect concentration (PNEC) is primarily applied to understand if the antibiotic concentration in the receiving water can create selection pressure in bacteria to develop resistance.

The pharmaceutical industry, however, highlights gaps in evidence that links the impact on human health that such discharge may have. Other gaps that are discussed in published literature include limited environmental field data from multiple locations and multiple samples, correlation between concentration of antimicrobials with that of antibiotic resistant genes or antibiotic resistant bacteria.[9,10]

Emerging consensus to act on antibiotics in manufacturing discharge

A consensus has been emerging among stakeholders that the current level of understanding and evidence is sufficient enough to act and contain antibiotic pollution from manufacturing and further evidence that is being generated can continue to inform action.

The Interagency Coordination Group (IACG) on AMR in its 2019 report, 'No time to wait: securing the future from drug-resistant infections' submitted to the United Nations Secretary General, recognised discharge of waste from pharmaceutical manufacturing as one of the drivers of AMR. It noted that, 'concerns about the impact of antimicrobial resistance on the environment and natural ecosystems are growing (among others) such as due to waste from pharmaceutical manufacturing despite limited evidence. Effective standards and practices in environmental protection and the proper management of pharmaceutical waste can further reduce the spread of antimicrobial residues along the food chain and in the environment'.[11]

The 2020 'Technical Brief on Water, Sanitation, Hygiene and Wastewater Management to Prevent Infections and Reduce the Spread of Antimicrobial Resistance,' jointly developed by the World Health Organization (WHO), Food and Agriculture Organization (FAO) of the United Nations and World Organization for Animal Health (WOAH; earlier known as OIE) recommends the reduction of releases of antimicrobials and antibiotic resistance genes (ARGs) into waterways from antimicrobial manufacturing as one of the action areas. The report cites evidence to show that inadequate waste management prevails along many supply chains in the local and international manufacture of antimicrobials; untreated wastewater and sludge discharges from antimicrobial production can be a hotspot for antibiotic resistance genes (ARGs) development; and high concentrations of antimicrobials downstream of active pharmaceutical ingredient manufacturing plants can select for AMR in the local environment. It also notes that, 'hotspots of extremely high concentrations of antimicrobials have been documented downstream of manufacturing sites in emerging economies but emission of residual drugs can be quite significant even in Europe, despite strong focus on surface water quality.'[12]

A 2022 summary for policymakers by the United Nations Environment Program (UNEP) on the environmental dimension of AMR notes that, 'environmental releases of active pharmaceutical ingredients are a critical driver of the development and spread of AMR in some parts of the world' and 'untreated pharmaceutical wastes and other stressors have been found at concentrations necessary to increase the abundance of antimicrobial resistant microbes and ARGs'.[13] The UNEP's report of 2023 titled 'Bracing for Superbugs: strengthening environmental action in the One Health response to antimicrobial resistance', recognizes pharmaceutical manufacture as a key economic sector affecting AMR in the environment. It notes that 'the untreated

discharge of pharmaceutical wastes is a key example of where antimicrobial and other selective agents in the environment are sufficiently high to select for resistant microorganisms and ARGs in-situ and increase abundance of resistant microorganisms'. [14]

In this document we aim to highlight key global developments aimed at containing antibiotic pollution from manufacturing to reduce the risk of antibiotic resistance and what needs to be done in India. First, it covers the growing global momentum through different approaches, including at the level of the Global Leaders Group on AMR, the WHO, the European Union (EU) and G7 nations. Then it captures in detail, India's role in global antibiotic supply chain, its antibiotic manufacturing sector, policies and practices related to waste management and pollution regulation.Towards the end, the report provides the way ahead in terms of what Indian policymakers, regulators, scientific community and India's pharmaceutical industry should consider doing to address antibiotic pollution from manufacturing discharge and reduce the risk of growing antibiotic resistance, a silent pandemic with a potential to cause unprecedented crisis.

SECTION A

GLOBAL DEVELOPMENTS

1. Global momentum to contain antibiotic pollution from manufacturing

1.1 A 'call to action' by the Global Leaders Group on AMR

In 2022, the Global Leaders Group (GLG) on antimicrobial resistance made a 'call to action' to improve the management of discharges into the environment that may contribute to the emergence and spread of AMR.[15] Recognizing that adequate measures to treat and safely dispose of waste are required, this was the first such call—comprising specific and comprehensive actions—made to countries and the manufacturing sector, in addition to the human health sector and food systems, for strengthened governance and oversight, improved surveillance and data availability, improved discharge management and research and development *(see Box: GLG call to action—'Reducing antimicrobial discharges from food systems, manufacturing facilities and human health systems into the environment)*.[16]

1.2. Environmental aspects of manufacturing in WHO Good Manufacturing Practices (GMP)

Good manufacturing practices (GMP) in the pharmaceutical sector were first formulated by the WHO in 1975. It is a system to ensure that medicines are consistently produced according to the quality standards. Most countries accept import and sale of medicines that have been manufactured through an internationally recognized GMP such as WHO GMP. Many countries formulate their own requirements for GMP based on WHO GMP. Others harmonize their requirements.[17]

In 2020, the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) acknowledged the importance of tackling AMR and adopted the 'Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance', which was revised by the WHO after consultations and comments on its initial version of 2018.[18]

The points-to-consider document had recommendations for antibiotic API and FPP manufactures for self-audit and inspectors while carrying GMP inspections. These recommendations were about the application of waste and environment-related clauses mentioned in different WHO GMP related texts such as WHO GMP for products: main

GLG CALL TO ACTION—'REDUCING ANTIMICROBIAL DISCHARGES FROM FOOD SYSTEMS, MANUFACTURING FACILITIES AND HUMAN HEALTH SYSTEMS INTO THE ENVIRONMENT'

Excerpts on general and specific action with regard to the manufacturing sector

Strengthened governance and oversight

- In the manufacturing sector specifically, countries should develop and implement legal and policy frameworks with a lifecycle approach for antimicrobials manufacturing, promote and develop balanced and staged environment policies and approaches to manage and regulate manufacturing facilities and support environmental inspections, incentivize industry for compliance and excellence, and develop national antimicrobial manufacturing pollution standards based on best available evidence, treatment technology and situational analysis, and strengthen the capacity of environmental authorities to conduct audits and monitor compliance.

Improved surveillance and data availability

- Countries should strengthen One Health surveillance including the discharge of antimicrobials and AMR determinants from manufacturing facilities. They should take into account the need to build on existing systems, cost-effectiveness, data comparability and key knowledge gaps relating to the fate, concentration and impact of discharges on the environment. Priority should be given to collecting data that can support targeted action and support the development of guidance on waste management approaches and antimicrobial discharge limits.
- Countries should promote industry data disclosure, transparency and public access to waste and wastewater management data and mitigation practices in order to build credibility and public confidence.

Improved discharge management

- Manufacturing companies should commit to prevention and management measures to minimize the impacts of manufacturing discharges into the environment. This can be done through effective waste management technologies and practices, adoption and implementation of the common antibiotic manufacturing framework and the proposed independent certification schemes of the AMR Industry Alliance.
- All stakeholders should evaluate options and support efforts to create an enabling environment that influences and supports investment through incentives and efforts in pharmaceutical waste management without jeopardizing access to antimicrobials. Such evaluations may include an assessment of sustainable procurement policies, inclusion of environmental considerations in good manufacturing practices, environmental risk assessment before antimicrobial authorization and an independent product-certification scheme.

Research and development

- International technical, financing and research and development organizations and partners should promote research and development into cost-effective and greener waste management technologies including methods to remove antimicrobial residues and other tools (e.g., climate sensitive incinerators and measurement technologies) and standardized monitoring methods, and support mainstreaming of best practices in process and waste management.

principles; WHO GMP for APIs; but specifically, WHO GMP for pharmaceutical products containing hazardous substances. It considered that antimicrobials could be hazardous and may pose a substantial risk of injury to health or to the environment upon being released into the environment through their action on microorganisms. In the case of GMP guidance related to hazardous products, the clauses reflected requirements related to risk assessment, environmental protection and effluent treatment.

In addition, the points-to-consider document outlined expectations from manufacturers, which include verification of application of requirements during onsite inspections and retaining documentation related to waste and waste management *(see Box: Expectations from manufacturers of antimicrobials).*

The document notes that 'in principle, GMP does not focus on the environmental aspects but given the lack of control in the downstream processes of manufacturing, medicines will

EXPECTATIONS FROM MANUFACTURERS OF ANTIMICROBIALS

Application of the requirements outlined in the different GMP clauses shall be verified during onsite inspections. In addition, manufacturers of APIs and FPPs should consider retaining documentation on the following:

- **A risk assessment for all contaminants** related to antimicrobial manufacturing, in the event that they are released into the environment, and the associated risk of development of resistant microorganisms;
- Based on the risk assessment, **waste-stream analysis** for each antimicrobial agent produced (at API and FPP product sites), which should be repeated if there is a change in production affecting waste streams;
- The **quantity and nature of the waste generated**, including the analytical data and documentation of analyses performed and their findings on the levels of antimicrobial agents or their precursors;
- **Regular reports** on the collection, treatment and disposal of waste and wastewater. The frequency should be risk-based and in line with local, regional or international regulatory requirements, as applicable;
- Information on the **methods used to treat the waste** should be documented to be effective for each specific antimicrobial or antimicrobial precursor. Analytical data demonstrating the conversion of these substances and their residues to non-hazardous waste materials should be available at the facility and be kept up to date;
- If effective waste treatment is not yet implemented for all waste streams resulting from the manufacture of each API or FPP, **documentation on a time-limited strategy** should be in place, with specified milestones for that implementation, specifying actions towards achieving treatment that significantly reduces the concentration of the antimicrobial substance or its precursor (and its microbial source, when relevant); and
- A rationale and risk assessment as to **why the manufacturer selected specific methods of decontamination** of manufacturing waste containing antimicrobials and/or their mitigation strategy.

lose their value and therefore the focus no longer should be only on the aspects of GMP that are directly linked to the quality of medicines. It is crucial for manufacturers and all stakeholders to take action in order to protect the efficacy of medicines.'

The Expert Committee however acknowledged 'the importance of ensuring collaboration between product and environment inspections and of not mandating the new expectations, to allow for regulatory authorities that may have no jurisdiction over waste and wastewater'. Earlier as part of discussions, it was decided to not revise the main text (of GMP) but to propose a more gradual approach.

The committee also urged the WHO Secretariat to assist national inspectorates and manufacturers in implementing the recommendations in the adopted points-to-consider document for manufacturers and inspectors.

1.3. Group of Seven (G7) nations recognize the need for discharge limits

The 2021 G7 summit in Cornwall, England, saw country ministers addressing various aspects of antibiotic pollution from manufacturing industries. The health ministers agreed to work with environment ministers, the AMR Industry Alliance and academia to agree on standards as a baseline and explore a joint pathway to action for their mainstreaming.[19] They agreed to consider privileging the purchase and/or reimbursement of antibiotics manufactured according to these agreed standards. They called upon the WHO to accelerate the adoption of changes to relevant GMP guidance sections applicable to waste and wastewater from antimicrobial production. They also called upon industry to take these standards into account as part of their environmental, social and corporate governance responsibilities.

The climate and environment ministers, in their earlier communique, had noted with concern that there are currently no international standards on safe concentrations of antimicrobials released into the environment, including from pharmaceutical manufacturing and committed to accumulating knowledge on AMR in the environment and working to develop and agree such standards.[20] The finance ministers' statement mentioned that G7 members, through procurement amongst other things, would seek to recognise the particular value of antimicrobials that respond demonstrably to an identified public health need.[21] While pursuing measures to encourage more sustainable antimicrobial drug development, G7 members may consider certain guiding principles such as maintenance of high manufacturing standards, adherence to high environmental standards, including the proper management of manufacturing waste and pollutants.

1.4. European Union (EU) plans to source medicines based on green manufacturing

The 2019 'European Union Strategic Approach to Pharmaceuticals in the Environment' notes that 'of particular concern are the indications that emissions from some antimicrobial manufacturing plants in third countries, some of which supply products for consumption also in the Union, could be contributing to the development and spread of antimicrobial resistance at the global level.'[22]

One of the areas identified for action in this report is to, 'support the development of pharmaceuticals intrinsically less harmful for the environment and promote greener manufacturing'. As part of this, the EU Commission is to 'discuss, with the relevant member State authorities, the possibility of using procurement policy to encourage greener pharmaceutical design and manufacturing' and encourage, through dialogue and cooperation, as part of the Union's external policies, action in third countries where pharmaceutical emissions from manufacturing and other sources are suspected of contributing to the global spread of AMR.' [23]

The progress report on actions suggest that cooperation mechanisms exist with the main producing third countries and can be used to raise concerns (e.g. bilateral dialogues with India and China). As part of the international dimension of the 'Pharmaceutical Strategy for Europe', the EU strategic approach will continue to be followed, including bilateral dialogues.[24]

The 2020 'Pharmaceutical Strategy for Europe' recognizes the environmental risk of AMR due to production, use, disposal of medicines as residues and waste products may enter the environment.[25] It outlines the need for action throughout the lifecycle of medicines to reduce resource use, emissions and levels of pharmaceutical residues in the environment. It mentions that public buyers should design smart and innovative procurement procedures, by improving aspects such as 'green production'. It aims to 'enhance resilience' such as through environmentally sustainable pharmaceuticals. One of the ongoing flagship initiatives is to engage with international partners through cooperation to ensure the quality and environmental sustainability of APIs imported from non-EU countries.

Apart from the EU, certain non-EU countries such as Norway and Iceland have also taken initiatives in this direction *(see Box: Norway, Denmark, Iceland—environmental criteria in procurement of pharmaceutical products).*

NORWAY, DENMARK, ICELAND—ENVIRONMENTAL CRITERIA IN PROCUREMENT OF PHARMACEUTICAL PRODUCTS

In Norway, the Norwegian Hospital Procurement Trust, which is responsible for the procurement of medicines in hospitals, released new environmental criteria for the procurement of pharmaceutical products in 2019. In the new procurement of antibiotics, environmentally friendly production will be weighted by 30 per cent as allocation criteria, as compared to cost effectiveness (50 per cent) and supply reliability (20 per cent). The Trust also recognizes that risk of development of bacterial resistance is an important factor for antibiotics in its Pharmaceutical Strategy.[26]

Further, in 2019, on behalf of the Norwegian, Icelandic and Danish authorities, Amgros in Denmark (a publicly owned company which procures medicines for Danish hospital pharmacies), Landspitali in Iceland (a leading hospital) and Norwegian Hospital Procurement Trust in Norway came together to form the first joint procurement that is being carried out in the pharmaceutical field for use in hospitals. In June 2021, apart from the price and security of supply, a third criterion—environment was added in the joint Nordic tendering procedures. The environmental criteria included documentation on environmental certification, description of the environmental policy and description of eco-friendly transport. The tendering procedure included 13 drugs, out of which nine were antibiotics. While Denmark is a part of the EU, Iceland and Norway are not.[27]

1.5. Sweden plans to procure and incentivize environmentally sustainable antibiotics

A. National initiative on 'environmental premium'[28]

The Swedish Medical Products Agency (MPA) in collaboration with the Dental and Pharmaceutical Benefits Agency (TLV) and the Swedish eHealth Agency, is working on an environmental premium within the Swedish pharmaceutical benefits system. This environmental premium is in its testing period depending upon which, Swedish MPA will further sharpen it, if need be. Antibiotics are also being focussed upon in this trial period.

This premium, is to be adapted as per the product-of-the-month system, which is aimed at generics, and is part of the Swedish national pharmaceutical benefits system. Currently, the price and possibility of delivery are considered while selecting the product-of-the-month. The premium is aimed to stimulate the companies to lower their price, which directly increases the sale of their product, making it the product-of-the-month benefiting the pharmaceutical company. It basically helps sell more products, which are manufactured sustainably.

In order to get the premium, a company will have to apply to the Swedish MPA, who will assess based on an established criterion, and approve the premium, if the criteria are met. The Swedish MPA has designed the criteria to qualify for the premium in such a way

that the entire production chain from the manufacturing of API to the manufacturing of pharmaceutical products is included, with a focus on risks linked to releases in the aquatic environment via outgoing wastewater. The two criteria that are to be met are:

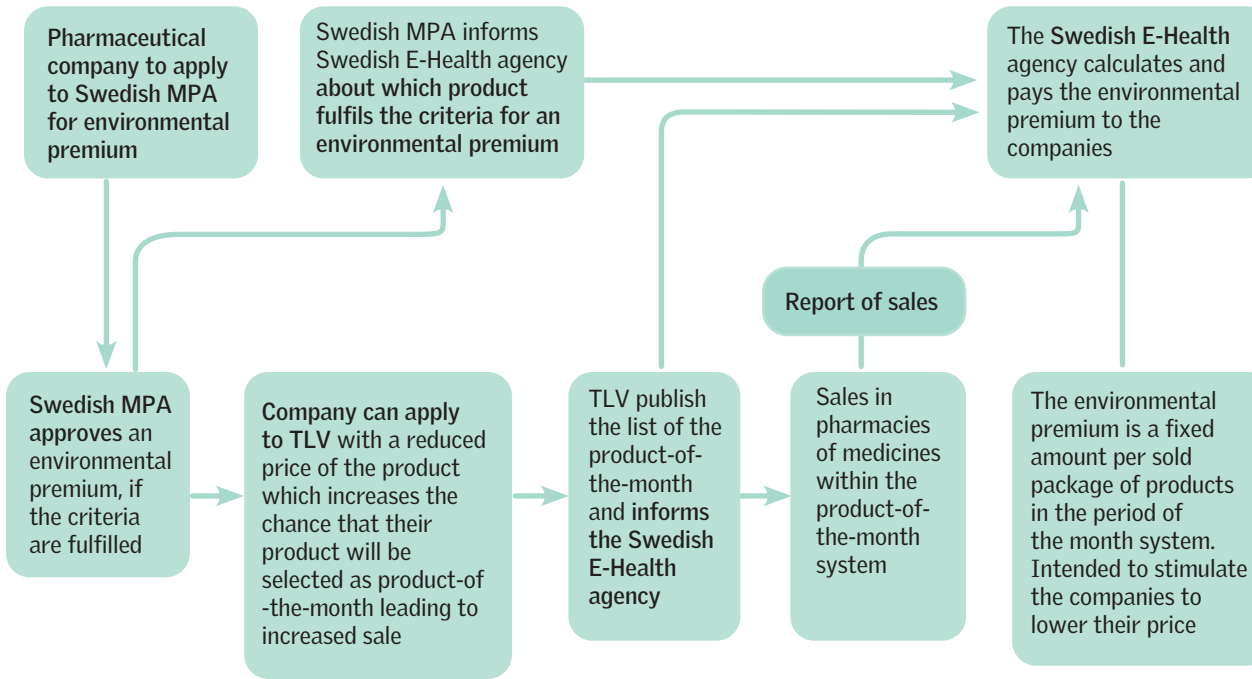
a. Fulfilment of requirements regarding the handling of waste containing API
b. Fulfilment of requirements regarding limit values or release of API into the aquatic environment

Once the premium is approved, the company then applies to the Dental and Pharmaceutical Benefits Agency with a reduced price of their product, so that the probability of the product being selected as the 'product-of-the-month' increases, leading to an increase in sale. After receiving the report of sales, the Swedish eHealth Agency calculates the premium, which is a fixed amount per sold package of products and gives it to the company. The premium will be available for all companies that sell medicines within the product-of-the-month system (not only Swedish companies) *(see Figure 1: Steps to get the environmental premium).*

B. Sustainability criteria for medicines by the Swedish National Agency for Public Procurement

Another national level initiative is the sustainability criteria developed by the Swedish National Agency for Public Procurement. The criteria exist for different areas including, nursing and care, of which medicines is a part. The criteria takes into account environmental and social considerations in public procurement.

Figure 1: Steps to get the environmental premium



The criteria uses three levels:

- **Basic/core**: criteria focused on reducing most of the environmental/sustainability impact linked to specific product area
- **Advanced:** criteria requiring a greater effort in following up, review evidence and evaluate the criteria
- **Spearhead:** procurer may need more specialist expertise and may need to devote more time to the verification work.

The user decides, with the help of available market information, ambition and needs, which level or levels to use. Under medicinal products, there are nine criteria, of which eight are linked to the environment. Based on the fulfilment of the criteria, tenders are awarded or special contract terms are applied *(see Table 1: Sustainability criteria for medicinal products under Swedish National Agency for Public Procurement).*[29]

Table 1: Sustainability criteria for medicinal products under Swedish National Agency for Public Procurement

Criteria	Level	Type	Purpose
Information about where (which country) pharmaceutical formulation takes place	Advanced	Award	To increase transparency and traceability when APIs are manufactured. Information provided on where APIs are manufactured for the medicinal products covered by the agreement allows contracting authorities to better identify environmental and social risks, and to prioritise follow-up efforts.
Information on the location of API production for medicinal products	Advanced	Award	
Information about the production facility in which pharmaceutical formulation takes place	Spearhead	Award	
Information about production facility in which APIs are manufactured for medicinal products	Spearhead	Award	
Available environmental information for medicinal products	Spearhead	Award	
Available environmental information for medicinal products	Core	Special contract terms	To ensure that suppliers implement procedures for identifying and managing the risk of active pharmaceutical ingredients (APIs) being released into the environment, so that the production of medicinal products should cause as little an environmental impact as possible.
Risk management procedures for environmental API emissions during the manufacture of medicinal products	Core	Special contract terms	
Sustainable supply chains	Advanced	Special contract terms	To ensure that the supplier has efficient risk management in their own operation and in the supply chain, covering the areas human rights, labour rights, environmental protection and anti-corruption.

Note: Award criteria are used to determine the tender to be awarded the contract when the award basis for the most economically advantageous tender is applied; Special contract terms are requirements which are imposed on the supplier or the product/service and are conditions that must be met during the performance of the contract

C. Antibiotic procurement criterion in Region Stockholm[30]

All 21 regions of Sweden procure pharmaceuticals on their own. In the Region Stockholm, which is the largest, a special criterion on the procurement of antibiotics aims to reduce emissions of antibiotics from manufacturing. The criterion does not contain any limits for the emissions of antibiotics, but the producer commits to sample the process wastewater (discharge) from the factory manufacturing the API, to analyze the concentration of the API in the water and report it to regional management office of the region. This criterion is the first step to collect data to set realistic concentration limits for antibiotics in process water. Further, it is recommended to consider the sustainability criteria for medicinal products under Swedish National Agency for Public Procurement while procuring antibiotics in the Region Stockholm. However, the region chooses to prioritize as it has its own criterion on emissions in the region.

2. Response of the AMR Industry Alliance to the crises of antibiotic resistance

In response to the AMR crisis, particularly the concerns related to manufacturing discharge, certain members of the global biopharmaceutical industry got together and the AMR Industry Alliance was created in 2017.[31] Over the years, the Alliance has been working in different areas to address AMR *(see Box: AMR Industry Alliance)*.

AMR INDUSTRY ALLIANCE

AMR Industry Alliance has over 100 members from biotech, diagnostics, generics and research-based pharmaceutical companies and associations. Sixteen are from the R&D pharma sector and nine are generic companies. Aurobindo Pharma Ltd. and Venus Remedies Limited are two Indian generic companies. Cipla and Globela Pharma Pvt. Ltd., are other Indian companies which were part this Alliance earlier.

Generics	R&D Pharma	
Athlone Laboratories	Boehringer Ingelheim	Otsuka
Aurobindo Pharma Ltd.	Clarametyx Biosciences	Pfizer Inc.
Centrient Pharmaceuticals	F. Hoffmann-La Roche AG	Sanofi S.A.
Fresenius Kabi AG	GlaxoSmithKline plc	Shionogi & Co. Ltd.
Recipharm	Johnson & Johnson	Sumitomo Pharma Co. Ltd.
Sandoz AG	Locus Biosciences	Menarini Group
Teva Pharmaceuticals, Ltd.	Merck & Co., Inc.	Oragenics, Inc.
Venus Remedies Limited	Merck	
Viatris	Novartis	

Source: AMR Industry Alliance Note: Information obtained from website, as on September 2023

2.1 Science-based PNEC targets for risk assessment

In 2018, the Alliance came up with the first science-based PNEC targets to guide environmental risk assessments. The discharge target can be derived using these PNECs and site-specific parameters. The discharge target can be equal to or less than PNEC targets. The Alliance urges member companies to work towards achieving these target values at the receiving water body.

The PNEC targets took into consideration two types of Predicted No Effect Concentrations (PNECs). One is PNEC-Environment (PNEC-ENV) intended to be protective of ecological

PNEC VALUES

PNEC is understood as the concentration of a given chemical substance (e.g., antibiotic) below which no adverse effects on ecosystems are expected to occur at any exposure time. The MIC, or minimum inhibitory concentration, is the lowest concentration of an antibiotic that inhibits the growth of a given strain of bacteria. In the AMR alliance PNEC targets, about 73 antibiotics have been assigned targets at sub-ppb levels.

If values for both—PNEC-MIC and PNEC-ENV—are available in studies, then the lower value is adopted as a target. If an antibiotic is not listed in the studies, a value of a similar antibiotic based on chemical structure or mode of action was made. Alternatively, if no data are available, a default PNEC of 0.05 µg/l was used. For example, for amoxicillin, the PNEC-ENV is 0.57 µg/l while the PNEC-MIC is 0.25 µg/l, and so the PNEC target taken by the AMR Industry Alliance for amoxicillin is 0.25 µg/l.[32]

The purpose behind taking the lower of the PNEC limits is that achieving these antibiotic discharge concentration targets will be both protective of ecological resources and also lower the potential for the evolution and selection of AMR in the environment.

species and the other is PNEC- Minimum Inhibitory Concentration (PNEC-MIC) values meant to be protective of resistance promotion. Both PNEC-ENV and PNEC-MIC values are adopted from the scientific published literature.[33, 34, 35] The updated 2023 PNEC targets for risk assessment are provided for 128 antimicrobials.[36] *(see Box: PNEC values).*

2.2 Antibiotic Manufacturing Standard and the certification scheme

In 2022, the AMR Industry Alliance released the 'Antibiotic manufacturing standard: Minimizing risk of developing antibiotic resistance and aquatic ecotoxicity in the environment resulting from the manufacturing of human antibiotics'.[37] The standard, facilitated by BSI Standards Limited, provides guidance to manufacturers in the global antibiotic supply chain to manufacture antibiotics responsibly, in order to minimize the risk of AMR in the environment.

This standard codifies and builds on the Common Antibiotic Manufacturing Framework (CAMF), released by the AMR Industry Alliance in 2018 that has established a set of minimum expectations and requirements from Alliance members. This standard is intended for use by the antibiotic manufacturer, as well as other pharmaceutical industry manufacturers, and stakeholders with an interest in antibiotic manufactures and their antibiotic suppliers, such as non-governmental organizations, academia, investors, buyers of antibiotics, and local and national governments.

ANTIBIOTIC MANUFACTURING STANDARD

The wastewater management program highlights:

- The general principle that the antibiotic concentration in the wastewater discharge should not increase the risk of AMR developing in bacteria in the environment. This can be ensured when the predicted environmental concentration (PEC), is less than the predicted no effect concentration (PNEC) resulting in the risk quotient to be less than 1. Wherein,
  i) PEC/PNEC= Risk Quotient (RQ) and RQ<1
  ii) PEC: Concentration of antibiotic in the receiving water (i.e. river, lake, ocean) resulting from a manufacturing discharge;
  iii) PNEC: developed by the AMR industry alliance shall be considered
- Demonstration of authorization/license/permit compliance such as through monitoring, assessment of compliance with authorization/license/permit to discharge treated wastewater, wastewater treatment and monitoring, record keeping and reporting
- Characterization of wastewater discharges by maintaining supporting documents, such as water balances, process flow diagrams and criteria for allowable discharge to wastewater
- Quantification and assessment of antibiotic discharges by measuring the risk quotient
- Control of routine discharges by employing good management practices and a hierarchy of control. Good management practices can be, for e.g., treating reject batches by collecting them on-site or off-site, maximizing closed transfers between process equipment to minimize spills, maximizing equipment dry cleaning, etc.
- Control of non-routine discharge by methods such as designing storage areas to prevent spills or releases into the environment.

The Alliance has also developed a certification scheme in collaboration with the BSI that will enable antibiotic manufacturers to demonstrate, through independent third-party evaluation, that waste streams containing antibiotic active pharmaceutical ingredient (API) and drug products are appropriately controlled during manufacturing by pharmaceutical companies. The certification scheme would have the potential to influence the entire supply chain, as every process (like API, packaging, formulation) would be separately certified. This scheme was released in June 2023 and one of the aims is to influence the decision of the procurement agencies, including government tenders *(see Box: Antibiotic Manufacturing Standard).*

The Alliance also publishes progress of its members. As per the latest progress report of 2022, out of 53 of the 93 members who participated in the survey, 76 per cent of antibiotic manufacturing sites owned by Alliance members and assessed against the CAMF fully met all framework requirements.[38] Most products manufactured at Alliance members' sites (88 per cent) were assessed against PNEC targets, and 87 per cent were found to meet these targets. However, 44 per cent of supplier sites were assessed against the CAMF, out of which 50 per cent met requirements fully; of products made at supplier sites, 42 per cent were assessed against PNEC targets, with 73 per cent of these meeting targets *(see Box: Common Antibiotic Manufacturing Framework).*

COMMON ANTIBIOTIC MANUFACTURING FRAMEWORK[39]

The framework was released by the AMR Industry Alliance in 2018. It described a risk-based approach to assessing and controlling antibiotic manufacturing waste streams. It provided a list of minimum expectations (e.g., compliance with local laws and regulations) and a set of minimum requirements (like quantification of antibiotics in process wastewaters, provision of effective wastewater treatments) from the Alliance members, along with some methodologies, all of which are needed to conduct a site risk evaluation of both large and small controls in the supply chains of the members. It detailed minimum expectations in the following areas:

- Regulatory compliance;
- Environment, health and safety management systems;
- Training;
- Waste and emissions, which highlights minimum expectations from two programs, water discharges and solid waste management;
- Site audits

The Antimicrobial Resistance Benchmark 2021 report of the Access to Medicine Foundation, which surveyed many of the research-based and generic manufacturers of the Alliance on different aspects, mentioned that pharmaceutical companies are making greater efforts to curb the release of wastewater containing APIs into local waterways, including by setting and enforcing discharge limits with their third-party suppliers. However, certain gaps remain in these endeavours.[40] While a few big companies are leading the way in tracking and asking for compliance from suppliers, overall, only 5.2 per cent of third-party manufacturing sites were reported as being compliant with limits on antibacterial waste disposal.

SECTION B

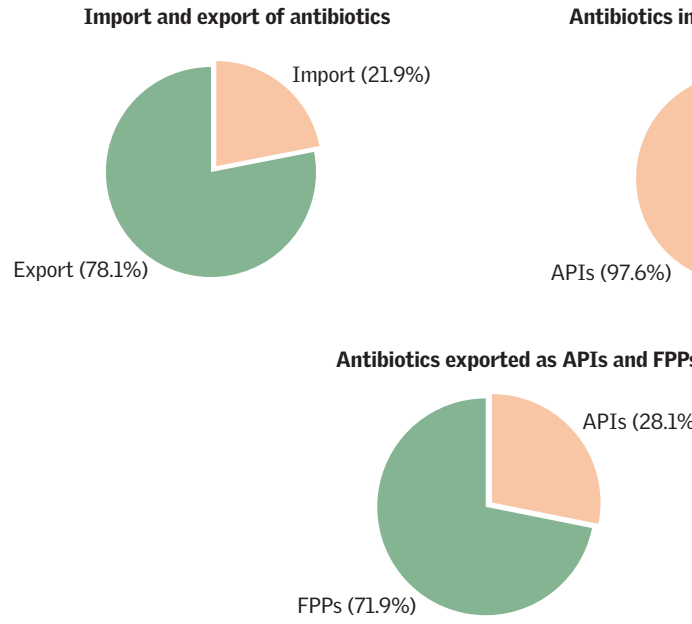
INDIAN SCENARIO

3. India as part of the global antibiotic supply chain

3.1 Antibiotic import and export[41]

In 2021–22, India imported about 32,567 metric tonne (MT) of antibiotics and exported about 1,15,911 MT. About 98 per cent of imports were antibiotic active pharmaceutical ingredients (APIs) and about 72 per cent of exports were finished pharmaceutical products (FPPs).[42] India exports mainly to low-and-middle income countries of Africa, Asia and Latin America, while it imports from different countries, with China being the largest API supplier *(see Figure 2: Antibiotic import and export in 2021–22).*

Figure 2: Antibiotic import and export in 2021–22



Note: Data for antibiotics exported or imported are obtained based on HS codes. HS codes are Harmonized System codes, a standardized numerical method of classifying traded products. Antibiotics are placed under two HS codes for the purpose of trade, which are HS code 29 (organic chemicals) and 30 (pharmaceutical products). Under HS code 29, HS code 2935 (sulphonamides) and 2941 (antibiotics) are APIs/bulk antibiotics. Antibiotics under HS code 30 are predominantly FPPs. Overall, HS codes up to 8 digits were analyzed.

Source: Export Import data bank (Annual), Department of Commerce, Govt. of India

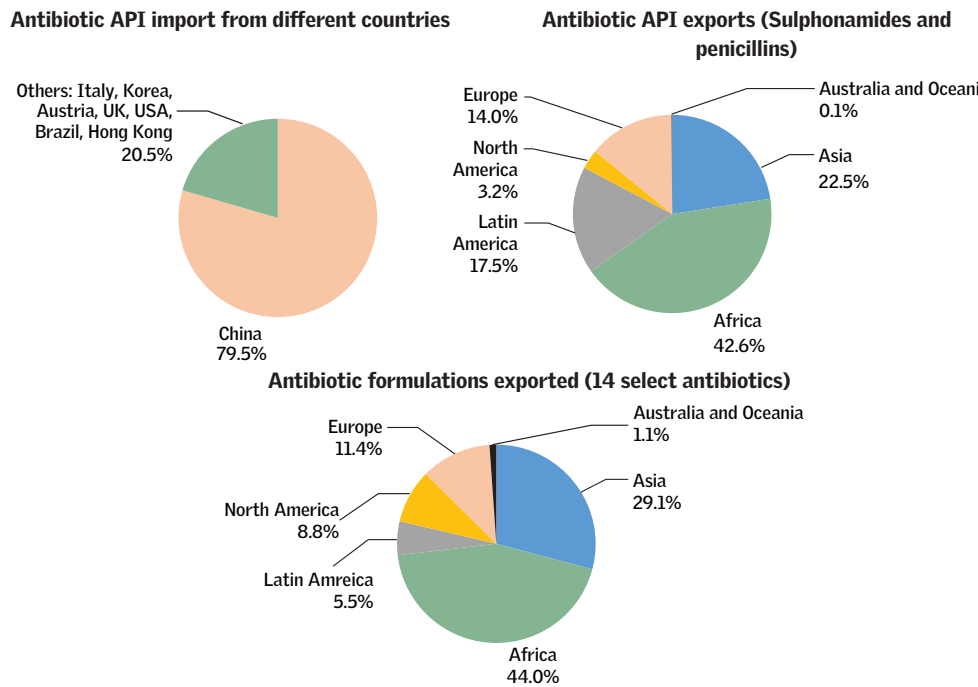
3.2 Antibiotic active pharmaceutical ingredients—import and export

The total amount of antibiotic APIs imported in 2021–22 was 31,786 MT. About 80 per cent of this was from China. The remaining 20 per cent was imported from countries like Italy, Korea, Austria, UK, USA, Brazil and Hong Kong *(see Figure 3: Import and export of antibiotic API and FPPs in 2021–22).*

Twenty-six different types of known antibiotics (their salts or derivatives) were imported, which belonged to nine different classes namely penicillins, sulphonamides, aminoglycosides, tetracyclines, amphenicols, macrolides, ansamycins, cephalosporins, and fluoroquinolones. The top two classes were penicillins (46.3 per cent) and sulphonamides (6.7 per cent). Penicillins were imported from 32 countries, with China contributing nearly 89 per cent of it, and the remaining came from Austria and United Kingdom. Of the different penicillins imported, amino-penicillinic acid (APA), an intermediate used to make penicillin or their derivatives is the highest imported within the class (about 46 per cent).

Sulphonamides were imported from 27 countries, with 89 per cent of it coming from China, while the remaining were from countries like Italy and Korea. About 30.9 per cent of the antibiotics imported are designated as 'other antibiotics'.

Figure 3: Import and export of antibiotic APIs and FPPs in 2021–22



Source: Export Import data bank (Annual), Department of Commerce, Govt. of India;

Note: List of 14 antibiotic formulations selected for region wise analysis and details of region wise exports are provided in Annexure 3

Table 2: Antibiotic APIs imported and exported in 2021–22

Antibiotic class	Import in MT (per cent of total antibiotic imported)*	Export in MT (per cent of total antibiotic exported)*
Penicillins	14,700.6 (46.3)	5,101 (15.6)
Other antibiotics	9,809.9 (30.9)	2820.6 (8.7)
Sulphonamides	2,118.0 (6.7)	22,687.1 (69.6)
Macrolides and ketolides	1,756.3 (5.5)	648.9 (2.0)
Tetracyclines	1,295.4 (4.1)	33.9 (0.1)
Ansamycins	840.5 (2.6)	113.7 (0.4)
Aminoglycosides	572.7 (1.8)	4.6 (0.01)
Fluoroquinolones	310.9 (0.98)	1,024.2 (3.1)
Cephalosporins	288.2 (0.9)	147.8 (0.5)
Amphenicols	94.3 (0.30)	37.5 (0.1)

*Values rounded off to one decimal place

Note: Total antibiotic API import in 2021–22 is 31,786 MT; total antibiotic API export in 2021–22 is 32,619.4 MT. Refer Annexure 4 for details

The total amount of antibiotic APIs exported out of India in 2021–22 was 32,619.4 metric tonne (MT), and included 31 different types of antibiotics across the same nine classes which were being imported. Sulphonamides (69.6 per cent) and penicillins (15.6 per cent) are the highest exported antibiotic APIs, together contributing about 85 per cent *(see Table 2: Antibiotic APIs imported and exported in 2021–22).*

Sulphonamide class are exported to about 128 countries, with Senegal (13.7 per cent), Colombia (10.4 per cent), and Netherlands (7.8 per cent) as top three countries.

Penicillins are exported to 86 countries, with top three countries being China (20.9 per cent), Thailand (12.2 per cent) and Nigeria (8.8 per cent). Among all penicillins, amoxicillin and its salts are the highest exported penicillin (55.3 per cent).

As sulphonamides and penicillins, collectively contribute to about 85 per cent (27,788.2 MT) of the total antibiotic APIs exported in 2021–22, a region-wise analysis for these two suggests that 22.5 per cent of the total penicillins and sulphonamides exported is sent to Asia, 42.6 per cent to Africa, 17.5 per cent to Latin America. African nations like Senegal, Ghana, Kenya, Nigeria and Egypt are some of the major procurers of these two APIs. Some Asian countries are China, Indonesia, Myanmar, Pakistan, Thailand and Vietnam. European countries also procure about 14 per cent of the two APIs.

Collectively, G7 nations procured about five per cent of both (1,404.38 MT), 98 per cent of which was sulphonamide. Overall, G20 nations (excluding India) procured about 31 per cent of both (8,540.92 MT), 79 per cent of which were sulphonamides.

3.3 Antibiotic finished formulation products—import and export

The total amount of FPPs, that include, for example, capsules, injections, ointments imported in 2021–22 was 780.9 metric tonne (MT). Twenty-three different types of formulations imported can be categorized across nine major classes namely, penicillins, sulphonamides, tetracyclines, macrolides and ketolides, cephalosporins, fluoroquinolones, nitroimidazoles, glycopeptides and lincosamides *(see Table 3: Antibiotic FPPs imported and exported in 2021–22).*

Cephalosporins were imported the most (37.1 per cent), from 17 countries and about 38.6 per cent of which came from the USA. Switzerland and Italy together contributed nearly 36 per cent of the imported cephalosporins.

A significant proportion (364.13 MT, 46.7 per cent of total import) imported are either not elsewhere specified or are categorized as other antibiotics. The next biggest antibiotic FPP imported is clindamycin, a lincosamide, which was imported completely from Belgium.

Table 3: Antibiotic FPPs imported and exported in 2021–22

Antibiotic class	Import in MT (per cent of total antibiotic imported)*	Export in MT (per cent of total antibiotic exported)*
Cephalosporins	289.6 (37.1)	18,499.3 (22.2)
Antibacterial formulations n.e.s	238.5 (30.6)	4,815.2 (5.8)
Others	123.7 (15.9)	7,553.4 (9.1)
Lincosamides	70.5 (9.0)	305.5 (0.4)
Penicillins	32.1 (4.1)	18,940.8 (22.7)
Macrolides and ketolides	9.9 (1.3)	3,196.9 (3.8)
Nitroimidazoles	9.7 (1.2)	13,059.5 (15.7)
Fluoroquinolones	2.5 (0.3)	8,544.3 (10.3)
Other antiTB drugs	1.8 (0.2)	1,727.7 (2.1)
Tetracyclines	1.0 (0.1)	1,339.7 (1.6)
Glycopeptides	0.4 (0.06)	644.3 (0.8)
Sulphonamides	0.2 (0.03)	3,358.8 (4.0)
Drugs used to treat TB		2,182.9 (2.6)
Amphenicols		4,32.5 (0.5)
Sulfa drugs n.e.s.		228.0 (0.3)
Polymyxins		86.9 (0.2)
Ansamycins		72.7 (0.1)
Aminoglycosides		29.5 (0.04)

*Values rounded off values to one decimal place; n.e.s. is not elsewhere specified; Note: Total antibiotic FPPs import in 2021–2022 was 780.9 MT; Total antibiotic FPPs export in 2021–2022 was 83,291 MT. Refer Annexure 5 for details

The total amount of antibiotic formulations exported out of India in 2021–22 was 83,291 metric tonne (MT). These primarily included formulations meant for retail sale (82,902.6 MT).

Overall, 49 different types of antibiotics across 14 major classes were exported. These include penicillins, aminoglycosides, cephalosporins, sulphonamides, tetracyclines, amphenicols, macrolides and ketolides, ansamycins, drugs used to treat tuberculosis, lincosamides, glycopeptides, polymyxins and nitroimidazoles. These classes cover about 82.8 per cent of the total quantity exported, whereas the remaining 17.2 per cent is categorized under sulpha drugs not elsewhere specified, other antitubercular drugs, antibiotic formulations not elsewhere specified and others where specifics are not provided.

Formulations of penicillins and cephalosporins classes are a big proportion (about 45 per cent) of FPPs exported. Within the penicillin class, the maximum commodity exported is 'other medicaments containing penicillins/derivatives thereof with a penicillinic acid structure/streptomycins or their derivatives put up for retail sale' (44.1 per cent). This is sent to 164 countries with the top three countries of export being USA, France and Ethiopia. The next highest exported penicillin is amoxicillin (41.2 per cent) sent to 135 countries, with Ethiopia, Iraq, USA and South Africa as top countries.

Within cephalosporins, about 92 per cent export is of other cephalosporins and their derivatives. Out of 155 countries to which it is exported, the top three countries are Nigeria, Yemen Republic and Ethiopia.

Out of the 49 antibiotics, 14 antibiotic FPPs which had a >1 per cent individual contribution to the overall export and collectively accounted for nearly 91 per cent of the total exports were selected for a region wise analysis. Out of the total quantity of these 14 antibiotics, 44 per cent were exported to Africa, 29.1 per cent to Asia, 5.5 per cent to Latin America, 8.8 per cent to North America and 11.4 per cent to Europe.

About 13.3 per cent were imported by G7 countries, and about 22 per cent were imported by G20 countries (excluding India and the EU).

4. Indian pharmaceutical manufacturing sector

India's pharmaceutical manufacturing industry ranked third in production during the year 2022–23.[43] During this time, pharmaceutical exports worth USD 23.5 billion and import worth USD 8.06 billion were made in 2021–2022. In 2019, Indian domestic pharmaceutical market size reached USD 20.3 billion.[44] The domestic anti-infective segment was about 14 per cent of the market share in 2020 and includes antibiotics, antifungals, antiprotozoals, anthelminthics, antivirals, and antimycobacterials.

There are about 500 API or bulk drug manufacturers which contribute by about eight per cent in the global API Industry. Ninety per cent of the WHO pre-qualified APIs are sourced from India. India manufactures about 60,000 different generic brands across 60 therapeutic categories, and is the largest supplier of generic medicines to more than 200 countries (20 per cent of global supply). As per 2021-2022 annual report of the Department of Pharmaceuticals, India had about 741 USFDA approved sites in August 2021.[45]

4.1 Antibiotic manufacturing hubs in India

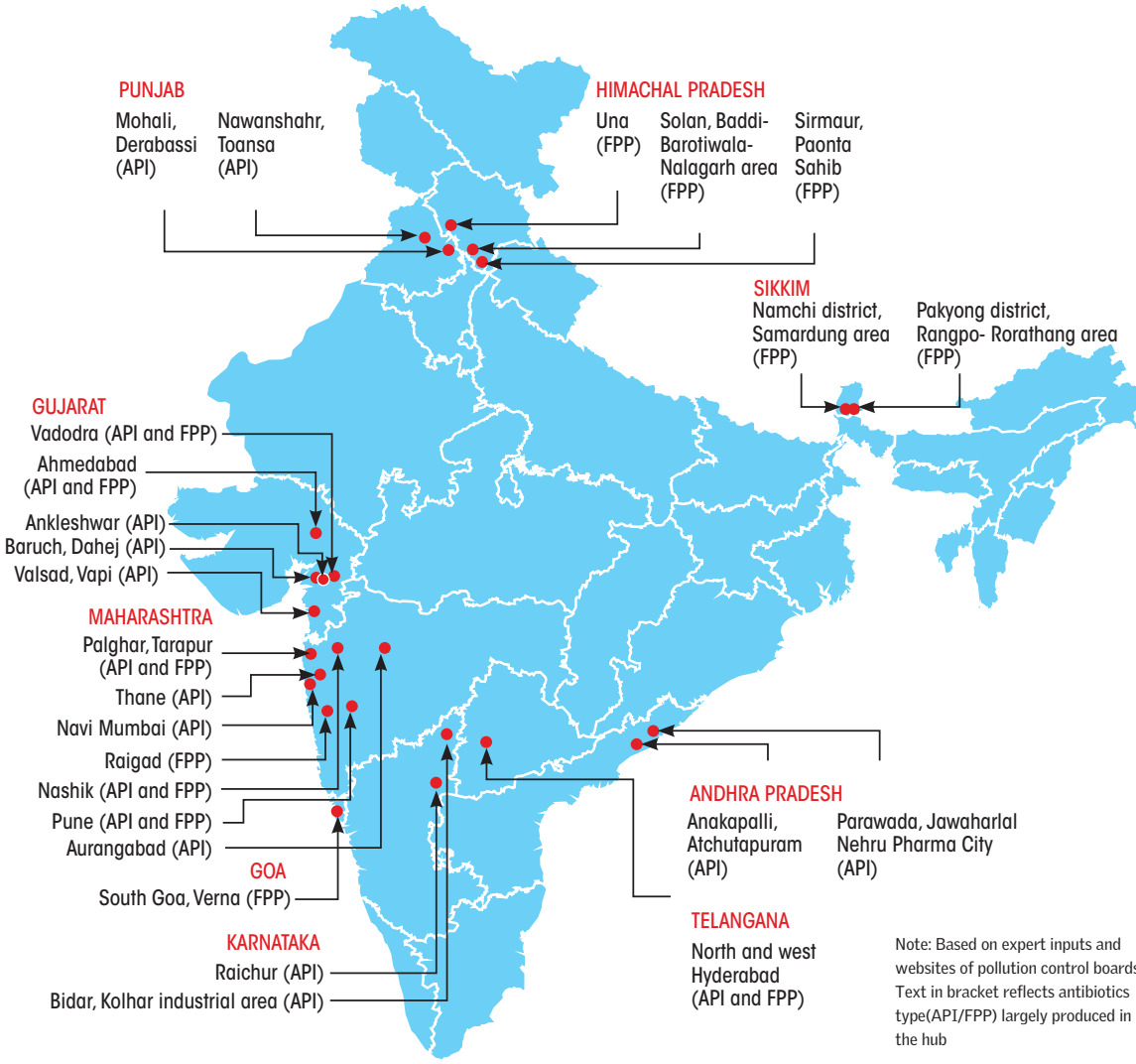
In India, the major antibiotic manufacturing is largely spread across 25 locations/hubs across nine states *(see Figure 4: Antibiotic manufacturing hubs in India)*

- Punjab and Himachal Pradesh in Northern India;
- Telangana, Andhra Pradesh and Karnataka in Southern India;
- Gujarat and Maharashtra in Western India;
- Goa in the South-west part of India;
- Sikkim in the North-eastern region

Most of the nine states have more than one hub with companies manufacturing antibiotics. With seven and five hubs respectively, Maharashtra and Gujarat have 12 out of 25 hubs. Hubs in Karnataka, Sikkim and Goa are relatively new.

Hubs in Himachal Pradesh, Sikkim and Goa are known to have companies largely manufacturing FPPs and those in Andhra Pradesh, Punjab, and Karnataka are largely manufacturing APIs. Hubs in Gujarat, Maharashtra and Telangana are known to have companies manufacturing both APIs and FPPs. There could be several hundred antibiotic manufacturing companies in these hubs. The exact number is not known *(see Box: Examples of companies manufacturing or marketing select antibiotic FPPs).*

Figure 4: Antibiotic manufacturing hubs in India



Note: Based on expert inputs and websites of pollution control boards; Text in bracket reflects antibiotics type(API/FPP) largely produced in the hub

EXAMPLES OF COMPANIES MANUFACTURING OR MARKETING SELECT ANTIBIOTIC FPPs

An understanding of the total number of antibiotic producers (APIs/FPPs), the kind of antibiotics they produce and the quantity, is not available in a consolidated form in public domain. Our interaction with stakeholders also indicates that such information is not available at one place anywhere. This could be more applicable for smalland- medium scale FPP manufacturers. Just to get a sense of the scale, a small exercise was conducted—through a mobile application typically used by pharmacists—to understand who manufactures or markets commonly used or prescribed antibiotic FPPs. It was found that about 380 companies were manufacturing/ marketing the 24 select antibiotics. Based on a random check, most of these appeared to be small-and medium-scale companies. This list however is not exhaustive and does not represent the total number of FPP manufacturers in India *(see Annexure 6: List of companies who manufacture or market select antibiotics in India).*

4.2. Policy framework on manufacturing and waste management

A. Good Manufacturing Practice requirements

The import, manufacture, distribution and sale of drugs in India is regulated as per the Drugs and Cosmetics Act 1940 and the Drugs Rules 1945.[46, 47] The Central Drugs Standard Control Organization (CDSCO) along with state drug departments are responsible for ensuring compliance to the Act and Rules.

The GMP mentioned under Schedule M of the Rules are required to be fulfilled in order to get license for manufacturing for sale or for distribution of drugs. It provides general and specific requirements for premises, plant and equipment for pharmaceutical products with regard to different types of formulations and active pharmaceutical ingredients (bulk drugs).[48]

Regarding waste management, GMP requirements suggests compliance with the local and/or national laws as follows:

- Sewage and effluents (solid, liquid and gas) to be disposed as per the requirements of the Environment Pollution Control Board
- Biomedical waste to be destroyed as per the BioMedical Waste (Management and Handling) Rules, 1996
- Rejected drugs should be stored and disposed with all the necessary precautions Hazardous, toxic substances and flammable materials should be stored as per guidance of central and state laws

A pharmaceutical manufacturing company is given a certificate of current Good Manufacturing Practice (cGMP) if it complies with Schedule M. However, if a company has to export, it needs a WHO-GMP certificate or a certificate of pharmaceutical product (CoPP), which is provided by the CDSCO after appropriate inspection.

B. Categorization of pharmaceutical industry based on pollution-causing potential

The Central Pollution Control Board (CPCB), state pollution control boards (SPCBs) and the Ministry of Environment, Forests and Climate Change (MoEFCC) collectively categorize an industrial sector as red, orange, green or white based on a pollution index (PI) score.[49]A higher value of PI denotes increasing degree of pollution load from the industrial sector. An industrial sector with a PI score of 60 and above is categorized as red, while those with PI score of 41–59 is categorized as orange. Those with PI score of 21–40 lie under the green category, and industrial sectors with PI score including and up to 20 will fall under the white category *(see Box: Scoring methodology to categorize industries).*

SCORING METHODOLOGY TO CATEGORIZE INDUSTRIES

The **scoring methodology** is based on the sum of three scores which are: water pollution score (W), air pollution score (A) and hazardous waste score (H).

- The water pollution score W is a sum of two scores, W1 and W2. W1 stands for score based on types of water-pollutants present in industrial processes wastewaters. There are seven categories under W1 (W11–W17), with each category linked to a particular type of discharge. The highest score of 30 is given to category W11 which applies to wastewater which is polluted and the pollutants are not easily biodegradable or toxic or both. W2 stands for score based on huge discharges of any kind and has a total score of 10. The maximum score of W is 40
- The air pollution score A is similarly a sum of A1 score (score based on types of air pollutants present in the emissions; maximum score 30) and A2 score (score based on consumption of fuels and technologies required for air pollution control; maximum score 10). The maximum score of A is 40.
- The maximum score for hazardous waste (H) is 20.

In the latest categorization released in 2016, the pharmaceutical industry, which includes API/bulk drug manufacturers, are categorized under the red category while the formulation industry comes under the orange category *(see Table 4: Scoring and categorization of pharmaceutical industry).*

Table 4: Scoring and categorization of pharmaceutical industry

Industry	Water pollution score			Air pollution score			Hazardous waste score		Category
	W1	W2	W (=W1+W2)	A1	A2	A (=A1+A2)	H	Total (W+A+H)	
Pharmaceuticals (API/bulk drugs)	30	10	40	30	5	35	20	95	red
Pharmaceutical formulation and for R&D purpose	20	-	20	20	-	20	15	55	orange

Source: Final document on revised classification of industrial sectors under red, orange, green and white categories, Central Pollution Control Board.

The total PI score for the pharmaceutical industry, that includes API/bulk drugs, is 95 out of 100. It has scored a maximum of 40 on water pollution (W), which is a sum of W1 and W2 score. This implies that the wastewater from the pharmaceutical industry has pollutants that are not easily biodegradable and/or toxic (based on W1 score) and that the industry has overall liquid waste generation of 100 kilolitres per day (KLD) or more, including industrial and domestic wastewater (based on W2 score). It has also received the maximum score of 20 for hazardous waste (H), and 35 out of 40 for air pollution (A).

The effluent generation of different pharmaceutical manufacturing units can vary significantly. For example, a large API can generate around 100 KLD of high TDS effluent (TDS above 5,000 mg/l) and around 300 KLD of low TDS effluent (TDS below 5,000

mg/l). High TDS effluent is generated during the processes, whereas low TDS effluent can be generated by things like vessel washing, floor cleaning, running utilities, etc. Similarly, a medium-scale formulation unit can generate around 30 KLD of low TDS effluent. Some small-scale formulation manufacturers can even generate effluent in the range of 1–2 KLD.

The CPCB further notes that the pharmaceutical industry sector (excluding the formulation industry) is the one among the '17 categories of Highly Polluting Industries' which can generate all sorts of pollution. These 17 industries are to be closely monitored and are required to have Continuous Online Emissions/ Effluent Monitoring Systems (CEMS) in place.[50] Moreover, red category of industries are also not normally permitted to operate in the ecologically fragile/protected area.

The PI score of the formulation industry is 55. Its water pollution score and air pollution score is 20 each. It has also received a hazardous waste score of 15. The scores clearly indicate that waste from pharmaceutical API/bulk drug industries is more problematic than waste from formulation industries.

C. Discharge standards for pharmaceutical manufacturing effluents in India

Waste from pharmaceutical manufacturing in India is regulated by the MoEFCC. The governing Acts and Rules are the Environment (Protection) Act, 1986, the Environment (Protection) Rules, 1986 and the Water (Prevention and Control of Pollution) Act, 1974.[51, 52] The responsibility of ensuring compliance with laws and regulations lie with the CPCB and SPCBs.

The standards for waste from pharmaceutical industry, which includes both bulk drug and formulation, are given by the Environment (Protection) Second Amendment Rules, 2021.[53] This Rule gives effluent standards, emission standards, limits for solvent losses and standards for managing chemical and biological sludge generated by the industry.

The effluent standards give both compulsory parameters such as pH, biological oxygen demand (BOD), chemical oxygen demand (COD), total suspended solids (TSS), as well as additional parameters such as phosphates, sulphides, zinc, copper, arsenic, mercury and lead. The Rule notes that the additional parameters shall be prescribed by SPCB as per the needs and discharge potential of member industries, and shall specify the frequency of monitoring considering the receiving environment conditions.

The effluent standards are applicable to all discharges being made into land and surface water bodies, including the use of treated wastewater for horticulture or irrigation purposes. However, it is not applicable to industry discharging to Common Effluent Treatment Plant (CETP) *(see Table 5: Effluent standards for pharmaceutical industry (Bulk drug and formulation)).*

As per the Rule, the total cumulative losses of solvent should not be more than five per cent of the solvent on an annual basis from storage inventory. The chemical and biological sludge generated from pharmaceutical manufacturing (bulk drug or formulation) should be regarded as hazardous waste and treated as per the Hazardous and Other Wastes (Management and Transboundary Movement) Rules, 2016. It is important to note that these effluent standards do not include antibiotics.

Table 5: Effluent standards for pharmaceutical industry (Bulk drug and formulation)

Parameter	Standards
	Limiting value for concentration (in mg/l except for pH and Bio assay)
Compulsory parameters	
pH	6.0–8.5
Biological Oxygen Demand (BOD, 3 days, 27°C, mg/l)	30
Chemical Oxygen Demand (COD, mg/l)	250
Total Suspended Solids (TSS, mg/l)	100
Oil and Grease (mg/l)	10
Ammoniacal nitrogen (mg/l)	100
Bio - Assay Test	90 per cent survival of fish after first 96 hours in 100 per cent effluent
Additional parameters	
**Benzene	0.1
**Xylene	0.12
**Methylene Chloride	0.9
**Chlorobenzene	0.2
Phosphates as P	5
Sulphides as S	2
Phenolic Compounds	1
Zinc	5
Copper	3
Total Chromium	2
Hexavalent Chromium (Cr6+)	0.1
Cyanide (as HCN)	0.1
Arsenic	0.2
Mercury	0.01
Lead	0.1
Sodium Adsorption Ratio (SAR)	Less than 26 (applicable only for discharge on land)

Source: Environment (Protection) Second Amendment Rules, 2021

**Limits shall be applicable to industries that are using benzene, xylene, methylene chloride, chlorobenzene

4.3 Limits for antibiotics in manufacturing effluents as proposed by MoEFCC in 2020

A. The draft standards proposed compared to notified standards

In view of actions planned in India's National Action Plan to contain AMR (2017–22), the CPCB started working to develop discharge standards for antibiotics in pharmaceutical effluents. In January 2020, the MoEFCC released the draft Environment (Protection) Amendment Rules, 2019 for bulk drug and formulation (pharmaceutical) industry for public comments.[54] The draft provided limiting values for concentration of antibiotic residues in the treated effluent of bulk drug and formulation industry, and CETPs with membership of bulk drug and formulation units. These values were developed by CPCB after consultations with relevant stakeholders including industry, scientific community and civil society.

The draft provided a list of 121 antibiotics. The limiting values of these antibiotics were based on PNEC values from published scientific literature.[55] This was also followed by factoring in a 60–90 per cent reduction efficiency of the wastewater treatment system in reduction of antibiotic residues (the reduction efficiency was arrived at by CPCB after assessing the efficiency of select manufacturing plant's effluent treatment plants (ETPs) in removal of antibiotic residues).

The draft had also clarified that the Zero Liquid Discharge (ZLD) system in bulk drug and formulation industry shall be considered when treated effluent, meeting the limits prescribed for compulsory parameters, is used in process or utilities (boiler/cooling tower etc.). The reuse of treated effluent in gardening/horticulture shall not be considered as ZLD in bulk drug and formulation industry. The draft further mentioned that the sludge containing antibiotic residues shall be incinerated and the standard of incinerator notified for common hazardous waste incinerator or industry-specific incinerator shall be applicable.

However, when the draft was finally notified in August 2021 as Environment (Protection) Second Amendment Rules, 2021, these limiting values for antibiotic residues were not mentioned *(see Box: Examples of additional changes in August 2021 notified standards from January 2020 draft).*

B. Antibiotic limiting values proposed in the draft compared to PNEC targets adopted by the AMR Industry Alliance

The PNEC targets of the AMR Industry Alliance are based on the same scientific literature referred to by the CPCB. However, on comparing the limiting values in this draft with the PNEC targets, values in the draft standards were found to be at least about 60 per cent less in most cases than the values given by the Alliance. In few cases, limiting values were relaxed than PNEC targets. This means that the overall draft standards, if notified, would have been more stringent as well as binding for the industry to follow *(see Table 6: Comparison of antibiotic limiting values proposed in the draft with PNEC targets adopted by the AMR Industry Alliance).*

EXAMPLES OF ADDITIONAL CHANGES IN AUGUST 2021 NOTIFIED STANDARDS FROM JANUARY 2020 DRAFT

- It did not include the text 'For the final outlet of ETP'
- It did not include the text 'ZLD = Zero Liquid Discharge system in Bulk Drug and formulation industry is considered when treated effluent meeting the limits prescribed for compulsory parameters shallbe used in Process or Utilities (boiler/ cooling tower etc.). The reuse of treated effluent in gardening/horticulture shall not be considered as ZLD in Bulk Drug and formulation industries', under Notes of section A on Effluent standards.
- It did not include the note,'The sludge containing antibiotic residues shall be incinerated and the standard of incinerator notified for common hazardous waste incinerator or industry specific incinerator shall be applicable' and mentioned that chemical and biological sludge from wastewater treatment or its management facility at industry or CETP shall be managed as per the Hazardous and Other Wastes (Management and Transboundary Movement) Rules, 2016.

Table 6: Comparison of antibiotic limiting values proposed in the draft with PNEC targets adopted by the AMR Industry Alliance

Active pharmaceutical ingredient	Limiting value for concentration (µg/l) as per 2020 MoEFCC draft standards	PNEC targets for risk assessment (µg/l) as per AMR Industry Alliance*	Per cent by which limiting values are less than PNEC targets
Itraconazole	0.004	not available	-
Amphotericin B, Anidulafungin	0.01	not available	-
Faropenem, Fidaxomicin	0.01	0.02	50.0
Azithromycin, Ceftriaxone, Neomycin, Trovafloxacin	0.01	0.03	66.7
Cefixime, Cefpirome, Ceftaroline, Ceftiofur, Ciprofloxacin, Enrofloxacin, Gemifloxacin, Meropenem, Retapamulin, Rifampicin, Phenoxymethylpenicillin, Sparfloxacin, Telithromycin	0.02	0.06	66.7
Delamanid	0.02	0.03	33.3
Bedaquiline, Clarithromycin	0.03	0.08	62.5
Cephalexin	0.03	0.21	85.7
Clarithromycin	0.03	0.25	88.0
Cefotaxime	0.04	0.12	66.7
Clindamycin	0.04	0.10	60.0
Doripenem	0.04	0.13	69.2
Cloxacillin, Ertapenem, Gatifloxacin, Imipenem, Isoniazid, Metronidazole, Moxifloxacin	0.05	0.13	61.5
Gentamicin	0.08	0.15	46.7
Ceftobiprole	0.09	0.23	60.9

Active pharmaceutical ingredient	Limiting value for concentration (µg/l) as per 2020 MoEFCC draft standards	PNEC targets for risk assessment (µg/l) as per AMR Industry Alliance*	Per cent by which limiting values are less than PNEC targets
Amoxicillin, Ampicillin, Benzylpenicillin, Cefdinir, Cefpodoxime, Ceftibuten, Flumequine, Levofloxacin, Mupirocin	0.10	0.25	60.0
Fluconazole	0.10	not available	-
Tildipirosin	0.17	0.42	59.5
Aztreonam, Cefaclor, Cefepime, Cefoperazone, Ceftazidime, Cefuroxime, Clinafloxacin, Erythromycin, Fusidic acid, Narasin, Netilmicin, Norfloxacin, Ofloxacin, Oxytetracycline, Piperacillin, Spiramycin, Teicoplanin, Trimethoprim	0.20	0.5	60.0
Sulfadoxine	0.24	not available	-
Sulfamethoxazole	0.24	6.6	96.3
Tylosin	0.33	1	67.0
Cefazolin, Daptomycin, Mecillinam, Minocycline, Oxacillin, Roxithromycin, Secnidazole, Tetracycline, Thiamphenicol, Tiamulin,Tobramycin	0.40	1	60.0
Tigecycline	0.40	0.1	-300.0
Tilmicosin	0.40	0.8	50.0
Kanamycin	0.44	1.05	56.0
Cefquinome	0.64	1.6	60.0
Lincomycin	0.72	0.81	11.1
Ceftolozane	0.76	1.9	60.0
Capreomycin, Cefalothin, Colistin, Doxycycline, Ethambutol, Florfenicol, Fosfomycin, Loracarbef, Viomycin, Virginiamycin	0.80	2	60.0
Cefadroxil	0.80	0.14	-471.4
Polymixin B	0.80	0.06	-1233.3
Cefaloridine	1.60	4	60.0
Enramycin	1.92	4.8	60.0
Linezolid	2.68	3.5	23.4
Avilamycin, Bacitracin, Cefoxitin, Chloramphenicol, Pefloxacin, Ticarcillin, Vancomycin	3.20	8	60.0
Tedizolid	3.92	3.2	-22.5
Amikacin, Nalidixic acid, Streptomycin	6.40	16	60.0
Sulbactam	6.40	not available	-
Cefalonium	8.40	21	60

Active pharmaceutical ingredient	Limiting value for concentration (µg/l) as per 2020 MoEFCC draft standards	PNEC targets for risk assessment (µg/l) as per AMR Industry Alliance*	Per cent by which limiting values are less than PNEC targets
Spectinomycin	12.80	32	60.0
Tazobactam	17.60	not available	-
Sulfadimethoxine	20.00	not available	-
Clavulanic acid	22.40	not available	-
Nitrofurantoin	25.60	64	60.0
Sulfadiazine	288.00	11	-2,518

*Source: AMR Alliance Science-based PNEC Targets for Risk Assessments (Revised 22 February 2023); draft 2020 MoEFCC standards;

Note:

1. Not available mentioned in case of antibiotics for which AMR Industry Alliance has not listed any values. According to the February 2023 AMR Alliance Science-Based PNEC Targets for Risk Assessments, if an antibiotic is not listed or no data are available, a default PNEC of 0.05 µg/l should be used.
2. (-) indicates not applicable as comparison cannot be made due to no values from AMR Industry Alliance.
3. Text in bold indicates – antibiotics wherein limiting values mentioned in MoEFCC draft were higher than the latest PNEC values.
4. The limiting value for concentration as per 2020 MoEFCC draft standards is applicable on the treated effluent from the outlet of bulk drug and formulation industry, and CETPs with membership of bulk drug and formulation units., while the PNEC targets for risk assessment as per the AMR Industry Alliance is to be achieved at the receiving water body.

C. Concerns raised by the Indian pharmaceutical industry and the AMR Industry Alliance on draft standards

In response to the notice for comments on draft 2020 MoEFCC standards, the industry associations shared their concerns. The AMR Industry Alliance also shared its point of view. *(see Table 7: Concerns raised by the Indian pharmaceutical industry and the AMR Industry Alliance on draft standards).*

The concerns were similar and primarily related to scientific rationale of the proposed limits/standards, applicability of these standards at the industry ETP outlet, technology to test and achieve proposed limits, applicability of standards for industry with zero liquid discharge units, incineration of sludge and time/capacity and infrastructure required for implementation.

It is noteworthy that both, the PNEC targets endorsed by the AMR Industry Alliance and the draft 2020 limits proposed by the MoEFCC, are derived from the same scientific literature (a 2016 publication by Bengtsson-Palme and Larsson),[56] but the key difference is that the proposed limits also incorporate reduction efficiencies of the effluent treatment plant (ETP). Therefore, these are, in most cases, atleast 60 per cent lower than PNEC targets.

The other difference is that PNEC targets developed by the AMR Industry Alliance apply on the receiving water body, whereas the limiting values of antibiotic residues proposed in the 2020 MoEFCC draft standards were applicable at the final outlet of ETP of the bulk and formulation industry, as well as CETPs.

Table 7: Concerns raised by the Indian pharmaceutical industry and the AMR Industry Alliance on draft standards

Issue/parameter	Indian Drug Manufacturers' Association[57]	Bulk Drug Manufacturers' Association, India^	AMR Industry Alliance^^
Scientific rationale of the proposed limits/ standards	Not in line with PNEC values of the AMR Industry Alliance; proposed limits arbitrarily lowered	Not science-driven and risk-based; not in line with industry initiatives taken	Need to include sound scientific rationale in establishing effluent standard limiting value concentrations for antibiotics
Applicability of the standards at the industry ETP outlet	Standards should not be applicable at the outlet of the individual industry ETP	Standards should not be applicable at outlet of individual industry	Standards should not be applicable at the ETP outlet; it should allow for subsequent mixing and dilution in the receiving body*
Technology to test and achieve proposed limits	No technology available to achieve the proposed limits	Limits specified in micrograms too low to be detected with standard HPLC test methods	Rule is silent on how to measure concentration of API to meet the standards
Applicability of standards for industry with ZLD units	ZLD units to be exempted from the proposed standards on all parameters related to effluents because ZLD units recover and recycle the effluents within utilities, has no environmental receptors	Industries with ZLD units should be exempted from following such standards as no water is discharged	Risks on reusing treated ZLD effluent in gardening/ horticulture to be identified and evaluated. If there is no risk to environment, its gardening/ horticultural re-use should be allowed
Incineration of sludge	More clarity on definition of sludge needed; API and pharmaceutical industry should be allowed to choose any options for sludge disposal as per Hazardous Waste Management Rules, otherwise mandating only them with incineration of sludge would be discriminatory	Industry may be allowed to continue with opting for landfill/incineration based on calorific value/use of cement plant facilities for co-processing	Definition of sludge be clarified; additional research needed to assess environmental impacts from land application of sludge; Risk-based approaches to sludge disposal/reuse recommended; Use of sludge as a fuel in commercial cement kilns be allowed subject to risk assessment
Additional comments- time, capacity, infrastructure required	Draft pushing for end-of-pipeline monitoring, over predictive/preventive control of pollution; Standards would be impossible to implement as it will cause deep distress to entire industry, push it to non-compliance, and make it prone to litigations and harassment by activists and regulators	Cannot be achieved in short-term due to required capital investment, facility and infrastructure enhancements, and required control technologies to meet the levels proposed	Highlighted the absence of timelines for industries to come into compliance, method used to measure API concentrations in complex wastewater matrices, frequency of measurement etc.

Source: Information available in public domain and received from industry. ^Information received from industry. ^^Information received from an AMR Industry Alliance member.

*As per the industry, internationally accepted approach incorporates a mixing zone in the receiving body of water to determine the acceptable discharge concentrations[58, 59]

D. National Green Tribunal order on antibiotic limiting values proposed in draft standards

In response to a petition filed with the National Green Tribunal (NGT) in 2020, the NGT ruled that the draft notification containing limiting value for concentration of antibiotic residues in the treated effluent of bulk drug and formulation industry, should be strictly followed by all concerned. The petition was filed by the Veterans Forum for Transparency in Public Life against the discharge of waste from the CETP at Baddi, Himachal Pradesh and from Acme Life Sciences, Nalagarh and Helios Pharmaceuticals, to prevent pollution of rivers Sirsa and Satluj.[60]

Taking cognizance of the serious consequences of unregulated discharge of API residues on the environment and public health, the NGT responded to the petition through its final verdict in April 2022.[61] The verdict stated that:

- Pending finalization by the MoEFCC, the proposed standards as per draft notification are to be strictly followed by all concerned
- The CPCB Guidelines on Monitoring Mechanism for API residues should be abided
- The SPCB may take further action accordingly to prevent and remedy the situation of unregulated discharge of harmful pollutants of pharmaceutical industries in the rivers
- CPCB may coordinate with the SPCBs to strengthen monitoring of API and assess Predicted No-Effect Concentration (PNEC) values
- ETPs and CETPs may be upgraded to control the discharge of active ingredient
- Ambient monitoring of recipient aquatic resources like rivers, lakes, ground water should be carried out
- CPCB and SPCBs may intensify monitoring of micro pollutants by regular vigilance

Following the final verdict of the NGT, the MoEFCC filed a review petition against this verdict in May 2022 with the NGT. The MoEFCC stated that the NGT final order is not called for since the standards in the draft notification have not been included in the final notification. This petition was dismissed by the NGT citing absence of merit in it and that the judgement was passed after due consideration.[62]

In November 2022, another execution application was made by the same petitioner for execution of the Tribunal's final order. According to the applicant, violations are still continuing despite the NGT order, and the MoEFCC is yet to take any action towards finalizing the standards. The NGT directed the MoEFCC and SPCB to take necessary remedial measures in accordance with the law.[63]

The NGT had earlier suggested in its interim orders:

- The constitution of a Joint Committee (comprising MoEFCC, CPCB, Himachal Pradesh PCB, District Magistrate, Solan) to look into the matter. It recommended the Joint Committee to conduct inspection of the area and submit a report *(see Box: Key findings from the final report of the Joint Committee submitted to the NGT in January 2022).*

KEY FINDINGS FROM THE FINAL REPORT OF THE JOINT COMMITTEE SUBMITTED TO THE NGT IN JANUARY 2022[64, 65]

- Himachal Pradesh PCB (HPPCB) monitored 210 pharmaceutical industries in Baddi-Barotiwala area, of which 111 were manufacturing antibiotics. Of the 111 antibiotic manufacturing companies, 37 were non-compliant with regards to the limits for discharge parameters prescribed for discharging into CETP. However, HPPCB could not take any action due to a stay order by the state High Court
- Twelve antibiotic manufacturing units were monitored for the presence of 20 antibiotic residues in effluent (treated and untreated). Residues were found at the outlet of industries leading to CETP (e.g., azithromycin, ciprofloxacin, ofloxacin, levofloxacin), and at outlet of CETP leading to Sirsa river (e.g., ofloxacin, levofloxacin)
- Other antibiotics were present at below quantification limits (BQL). But it should not be considered as an absence of antibiotic residues because the quantification limit of analysis (1 ppb) in the lab engaged for this analysis was 2–300 times more than the PNEC of different antibiotics.[66] Here, PNEC is the concentration of the antibiotic, which mark the limit, below which no adverse impact on the ecosystem is measured
- Since MoEFCC has notified standards for pharmaceutical industry in August 2021 with no mention of limits for antibiotic residues, there was no parameter which the Joint Committee could use for comparison of results
- The Joint Committee recommended that all pharmaceutical industries of BBN area may be connected to CETP Baddi and the "limit of antibiotic residues as BDL/<PNEC" may be incorporated by SPCB as one of the terms of 'consent to operate' granted to CETP Baddi, after commissioning the proposed add on facility

The report also captures action taken by HPPCB against the violations. The state board acknowledged that the issue of antibiotic residues in effluents is relatively new with no evidence, expertise or standards available with the board. It had constituted two internal committees to examine the issue and prepare a proposal of standards for antibiotic residual discharge and to finalize the total requirement of instruments/facilities needed for analysis of antibiotics in effluents. The HPPCB has recommended and repeatedly requested the MoEFCC to notify the standards of API and antibiotic residues in effluent at national level through several letters, but the final notified standards did not include these limits. It has also directed drug manufacturing units to ensure that adequate treatment facility be provided by all pharmaceutical industries for treatment of antibiotic residues and reduce these residues in discharge.

- That CPCB may suggest a monitoring mechanism for API residues for all pharmaceutical industries in the country discharging API residue directly or indirectly in river systems.

E. The NGT case verdict in the Supreme Court of India

In October 2022, the case was moved to the Supreme Court where it was highlighted by the appellant, that 'looking into the complexity and non-availability of any universally accepted standardized method to test API/AMR, it was proposed to remove the proposed norms of API/AMR from the additional parameters and after active consideration consciuosly it was not incorporated when the final Notification came to be notified on 06.08.2021.'

'In the given facts and circumstances, the direction of Tribunal to continue with the draft Notification so far as API/AMR is concerned, needs to be interfered by this Court.'

A stay on operation of impunged orders of NGT has been placed (orders dated 06.04.2022 and 24.05.2022).[67]

The matter was called for hearing again on February 6, 2023 and on March 20, 2023.[68, 69] As per the current update on the website of the Supreme Court, in the hearing carried out in March, where the appellant was the Union of India, and the respondent is the Veterans Forum for Transparency in Public Life & Ors., the Court had given time to file information/ counter affidavit etc. As per the July 7, 2023 order, the affidavits and counter affidavits received from respondents on this matter are to be listed before the Honourable Judge for necessary directions.[70]

F. CPCB guidelines for monitoring mechanism for API residues and recommendations

In January 2022, the CPCB released guidelines for monitoring mechanism for API residues and recommendations, and shared it with the SPCBs. This guideline outlines detailed requirements for the analysis of antibiotic residues, frequency of monitoring as well as duties of SPCBs and Pollution Control Committees (PCCs). It has also validated the method of 21 pharmaceutical compounds with Limit of Quantification (LoQ), of which 18 were antibiotics. In addition, the CPCB has also provided recommendations for mitigation of AMR in the environment, and for reducing the input of antibiotics into the environment.[71]

The recommendations for the latter include:

- Antimicrobials manufacturing industry should possess a valid authorization for discharge of treated effluent. Compliance with each condition in the authorization should be achieved.
- Levels of antibiotic in process wastewater should be quantified e.g. mass balance.
- Wastewater sources from operations should be characterized and evaluated for treatability and control.
- Effective wastewater treatment plant is equipped with primary, secondary and tertiary treatment which is efficacious to eliminate the residual antibiotics. Industries may use deactivation techniques like acidification, neutralization to degrade active antibiotics moiety.
- Best practices during manufacturing process to minimize emission of antibiotics into water stream to reduce the influx into wastewater treatment plant or environment adopted.
- The CETP, wastewater treatment plant infrastructure, design and its effectiveness i.e. onsite, offsite and infrastructure and performance of treatment system before discharging to common effluent treatment plant, are to release the emission of residual antibiotics into environment.

- Sludge from process wastewater treatment should be managed in compliance with all local regulations. Assessments to be conducted to determine potential risk from sludge application to land.
- Systems and best practice guidelines to correctly dispose unused medicines should be set up.
- Use of antimicrobials, especially critically important ones should be limited.
- Frequent sampling is important to understand the levels of API residue in the discharge.
- Samples are collected, stored, and analyzed with results reported in accordance with regulatory requirements.
- Process areas (e.g., tanks, container storage areas, and process sewer systems) are designed, constructed and operated to prevent spills or releases antibiotic residue to the environment. Treatment systems should be in place to prevent soil, surface water, or groundwater contamination.
- Waste classification, labelling, storage and disposal methods should be in accordance with the hazard, characteristics of the waste, and in accordance with regulatory requirements. i) Waste containers are labelled with contents, hazard characteristics (e.g., flammable, biological), and closed once waste is placed in the container. ii) Disposal methods are based on waste characteristics. Records (e.g., waste classification determinations including analytical results, letters from waste contractors/facility, and certificates of destruction) are maintained.
- Waste disposal contractors/facility should possess authorizations/certifications from SPCBs/PCCs to manage specific waste streams in accordance with regulations.

5. Pollution Regulation in India

5.1. Industry practices to manage discharge

Based on the discussion with expert stakeholders and responses from 14 antibiotic manufacturers (four large and 10 small-and medium-scale) related to approaches/ technologies used to minimize antibiotic losses in wastewater, it is clear that waste management approaches adopted by companies depend upon multiple factors, which include:

- Nature and scale of operations i.e. APIs or FPPs
- Type of antibiotic (s) manufactured and quantity and/or quality of waste generated
- Infrastructure available for a technology/approach and associated cost of installation and maintenance
- Efficiency and effectiveness of the technology and its compatibility with existing system
- Legal/expected requirements such as related to discharge targets
- Need/preference for water recovering technologies
- Awareness and preference towards waste management and environment health and safety
- Commitments made as part of any alliance such as the AMR Industry Alliance

Each company follows a unique set of approaches, presumably based on the above set of factors to a large extent. However, it is also clear that overall, there is a pattern, in terms of difference in the way large and small/medium-scale companies approach waste management. Large scale companies also claim to focus on process control measures, in addition to resource-intensive waste management technologies/approaches. Similarly, there is also an apparent difference between API and FPP manufacturers *(see Table 8: Summary of responses from select antibiotic manufacturers).*

For example, in the case of large-scale antibiotic manufacturers, the waste management method commonly claimed to be used is the zero liquid discharge (ZLD) technology, which means that there is no discharge outside the manufacturing facility. These companies include Aurobindo Pharma Ltd., GlaxoSmithKline, Sun Pharmaceutical Industries Ltd. and Centrient Pharmaceuticals. The permeates generated in the ZLD process are either used within utilities such as in cooling towers/boilers or for gardening/ horticulture purposes. The sludge is usually incinerated or sent to the Treatment, Storage, and Disposal Facilities (TSDF) for disposal. While Centrient Pharmaceuticals responded that it achieves ZLD by making use of mechanical vapour compressor and agitated thin film driers (ATFD),

Sun Pharma shared that all antibiotic effluents are segregated into concentrated and lean effluent stream. The concentrated stream is passed through stripper, multiple effect evaporator (MEE) and ATFD for treatment and drying; dried salts as hazardous waste are sent for co-processing/pre-processing/disposal. The segregation of streams based on high and low TDS is a practice often adopted by API manufacturers.

Other than ZLD, few companies also mentioned the use of some advanced methods. For example, Aurobindo, apart from deactivating API residues in process wastewater, also mentioned about using membrane bioreactors.

In the case of small and medium pharmaceutical manufacturers, most commonly used approach is to send the primary treated waste to the CETPs. This is because within the industrial clusters, it is more cost-effective for them to send their effluents to a CETP. The companies are required to pay the CETP for collecting and treating their effluents. While majority of the companies (e.g., Saar Biotech, Zeiss Pharmaceutical Pvt. Ltd., Nikvin Healthcare India Pvt. Ltd., Helios Pharmaceuticals Pvt. Ltd.), shared that they follow primary treatment of their wastewater before sending to the CETP, few fail to do so because of limited infrastructure to treat effluents in-house at the primary ETP. Often, the CETP accepts wastewater which is not primary treated by charging the industry a higher rate for treating their effluent.

In some cases, the manufacturers have utilized a combination of technologies. For example, deactivation with sodium hydroxide/sodium hypochlorite is often carried out along with primary treatment before sending wastewater to the CETP. This was being said to be done by Unichem Laboratorites Ltd., Globela Pharma Pvt. Ltd., Zeiss as well as Helios.

Some medium and small manufacturers have installed reverse osmosis (RO) instead of installing the entire ZLD infrastructure. For example, Dagon Pharmaceuticals Pvt. Ltd. have installed only the RO as their effluent does not have TDS> 25 mg/l. It mentioned that this cost-effective solution treats the waste in an efficient way without additional infrastructure.

With regard to process control, most large-scale companies mentioned about adopting mass balance and measures that help optimize product recovery such as spill control, mopping instead of floor washing etc. Most small-and medium-scale companies did not give any specific response on process control measures.

Table 8: Summary of responses from select antibiotic manufacturers

Company	Process control measures claimed to be adopted	Waste management technologies/approaches claimed to be adopted
Large scale manufacturers		
Centrient Pharmaceuticals (API and formulation)	Mass balance	• Zero Liquid Discharge systems employed. This includes Mechanical Vapour Recompression, Agitated Thin Film Drier • Biological treatment • Tertiary treatment (Nano filtration followed by Reverse Osmosis)
Aurobindo Pharma Ltd. (API and formulation)	Mass balance	• Zero Liquid Discharge systems employed • Deactivation of API residues in process wastewater Membrane bioreactors
GlaxoSmithKline (Formulation)	Mass balance	• If antibiotic losses are higher than PNEC values, then wastewater is analyzed • Zero Liquid Discharge systems employed; treated effluent used for gardening purposes
Sun Pharmaceutical Industries Ltd. (API and formulation)	Mopping in place of floor washing to generate less effluent All powder processing equipments cleaned by dry mopping, vacuum cleaning to avoid antibiotic entering in wastewater stream	• Process effluent from operations is treated by means of specialized agents and bacteria that disintegrate the residual antibiotic product, which is further passed through double Reverse Osmosis process thereby ensuring absence of product in the treated effluent water • Facilities manufacturing the antibiotics are qualified as Zero Liquid Discharge facilities (having stripper, multiple effect evaporators, agitated thin film dryers, reverse osmosis) • Dried ATFD salts as hazardous waste sent for co-processing/pre-processing for disposal • Permeate from Reverse Osmosis used in boiler and cooling tower makeup • Any antibacterial residue and/or hazardous waste (emerging from recovery plant) are sent to government authorized incineration site for disposal (incineration and co-processing)
Small-and medium-scale manufacturers		
Dagon Pharmaceuticals Pvt. Ltd. (Formulation)*	Company ensures maximum recovery of API during the manufacturing process	• Reverse Osmosis system • If wastewater TDS is >25, it is reprocessed, sludge incinerated
Helios Pharmaceuticals Pvt. Ltd. (Formulation)	Site has adequate and appropriate control to monitor and reduce the entry of antibiotics into waste/effluent	• Standard Operating Procedure in place to handle waste/ effluent disposal at site • Effluent treatment plant comprising of oil & grease trap, equalization, clarification, chemical treatment followed by tube settler and biological treatment, settling and then finally tertiary treatment comprising of two stage sand and activated carbon filters. Final treated water is transferred to CETP through pipe line for disposal • Automatic 'dosing pump' is installed to maintain the sodium hypochlorite (40 per cent) as a treatment to eliminate the antibiotic residues

Note: *The practices mentioned are based on site visit/discussion with representatives of these companies located in Baddi. This does not cater to process control or waste management methods being used in any other site, which is not in Baddi.

Company	Process control measures claimed to be adopted	Waste management technologies/approaches claimed to be adopted
Saar Biotech (Formulation)*	-	• Effluent sent to CETP
Zeiss Pharmaceutical Pvt. Ltd. (Formulation)	Company ensures maximum recovery of API during the manufacturing process	• Primary and secondary treatment of wastewater followed by sending to CETP • Sodium hydroxide added to wastewater to deactivate beta-lactam ring before sending to CETP
Nectar Lifesciences Ltd. (API and formulation)**	-	• Use of Zero Liquid Discharge approach in the API facilities. • Permeate from RO used in utility purposes like cooling towers
Unichem Laboratories Ltd. (API and formulation)*	-	• Deactivation with sodium hydroxide followed by primary treatment and sending the treated effluent to CETP
Neuland Laboratories Ltd. (API)	-	• Use of Zero Liquid Discharge approach
Nikvin Healthcare India Pvt. Ltd. (Formulation)*	-	• Primary treatment of wastewater followed by sending to CETP
Globela Pharma Pvt. Ltd. (This is till April, 2022) (Formulation)	-	• Deactivation with sodium hydroxide followed by primary treatment. A residence time for few hours is given to ensure maximum deactivation of beta lactam ring. The treated effluent is then sent for ZLD.
Akums Drugs and Pharmaceuticals Ltd. (API and formulation)	Automatic system, mass balance	• Primary, secondary, tertiary treatment of wastewater; using treated water in horticulture • Units that are close to a CETP are sending wastewater to CETP for further treatment

*The practices mentioned are based on site visit/discussion with representatives of these companies located in Baddi. This does not cater to process control or waste management methods being used in any other site, which is not in Baddi.

**Practice information based on manufacturing plant operating in Dera Bassi, Punjab. (-) represents that this aspect could not be satisfactorily discussed

Note: CSE researchers reached out to about 21 small, medium and large scale manufacturers of antibiotic API or formulation or both. This was done using different approaches such as email-based questionnaire survey, telephonic discussion and in-person meetings (carried out over physical/virtual modes). In some cases, responses were not received in response to emails, but verbally when the company was separately reached out. The discussions were conducted in two rounds in 2021 and in 2022. Overall, responses were obtained from 14 companies. The attempt has been to capture the relevant part of the discussion/communication as shared by the respondent. The responses have not been verified by CSE.

5.2 Common effluent treatment plants in antibiotic manufacturing hubs

Due to the limited size and scale of operations of small-and medium-scale companies, installing individual ETPs is often not economically viable. In such cases, Common Effluent Treatment Plants (CETPs) have been set up in the industrial hubs, where clusters of small scale industrial units of different industries which can pollute are located. These companies collectively send their wastewater to the CETPs for treatment.[72]

The operation of a CETP is similar to that of a conventional ETP. CETPs help reduce the treatment cost to be borne by an individual unit while disposing off their effluents and protecting the environment. It also helps facilitate better monitoring by pollution control regulators. Individual units are expected to send effluents to a CETP after preliminary treatment.[73]

In India, the MoEFCC has been implementing a centrally sponsored scheme for CETPs since 1991. This scheme was to enable small-scale industries (SSI) set up CETPs in the country for installation of pollution control equipment for treatment of effluents through subsidies from the state and centre along with contribution from entrepreneurs and loans from financial institutions. The guidelines for central assistance to CETPs was revised in 2011 taking into consideration operational deficiencies in the earlier scheme and in the development of pollution control technologies and the recommendations of SPCBs.[74]

Out of the 25 antibiotic manufacturing hubs across nine states, 16 hubs across six states have a total of 35 CETPs of varying capacities ranging from 0.5–55 million litres per day (MLD). While many hubs have multiple CETPs, but Sikkim, Punjab and Goa, with five hubs in total, do not have any CETP in their antibiotic manufacturing hubs. The two hubs in Himachal Pradesh, one in Maharashtra and one in Karnataka also do not have any CETPs *(see Table 9: Antibiotic manufacturing hubs and CETPs in India).*

Out of 35 CETPs only four have wastewater recovery systems. This is similar to ZLD systems in companies wherein water is not discharged into the external environment. One is in Telangana (capacity: 5 MLD), two are Ahmedabad, Gujarat (capacity: 4.5 MLD and 16 MLD) and one in Bidar, Kolhar industrial area of Karnataka (capacity 0.5 MLD).

As per an RTI response from CPCB, there are 196 CETPs operational in the country, two of which cater solely to effluents from the pharmaceutical industry and 45 are equipped with water recovery systems. This means, at least 35 out 196 CETPs and four out of 45 with wastewater recovery systems cater to antibiotic manufacturing units.

Table 9: Antibiotic manufacturing hubs and CETPs in India

State	Hub location/ district/ region	Hub largely manufacturing (API/FPP/API and FPP)	No. of CETP(s)	Company managing CETP (capacity in MLD)	Waste water recovery system
Himachal Pradesh	Solan, Baddi-Barotiwala-Nalagarh area	FPP	1	Baddi Infrastructure (25)	No
	Sirmaur, Paonta Sahib	FPP	-	NA	NA
	Una	FPP	-	NA	NA
Punjab	Mohali, Derabassi	API	-	NA	NA
	Nawanshahr, Toansa	API	-	NA	NA
Telangana	North and west Hyderabad	API and FPP	2	Patancheru Enviro Tech Ltd. (2)	No
				Jeedimetla Effluent Treatment Ltd. (5)	Yes
Andhra Pradesh	Anakapalli, Atchutapuram	API	1	Atchuthapuram Effluent Treatment Plant (1.5)	No
	Parawada,Jawaharlal Nehru Pharma City	API	1	Ramky Pharma City (India) Ltd. (7)	No
Maharashtra	Palghar, Tarapur	API and FPP	1	Tarapur Environment Protection Society (50; 25 MLD operational)	No
	Nashik	API and FPP	-	NA	NA
	Navi Mumbai	API	2	Thane-Belapur CETP (27)	No
				Taloja CETP (22.5)	No
	Thane	API	5	Dombivli CETP (1.5)	No
				ACMA - CETP-Co-operative Society Ltd. (0.25)	No
				Badlapur CETP Association (8)	No
				Dombivli Better Environment System Association (16)	No
				Chikhloli-Morivali Effluent Treatment (0.8)	No
	Aurangabad	API	1	SMS Waluj CETP Pvt Ltd. (10)	No
	Pune	API and FPP	5	Kurkumbh Environment Protection Cooperative Society (1)	No
				Ranjangaon CETP (3)	No
				Greenfield CETP Pvt Ltd.^ (1.5)	No
				Hydro Air Tectonics (PCD)^ (4)	No
				Akkalkot CETP (3)	No
	Raigad	FPP	3	PRIA CETP (I) Ltd. (15)	No
				MMA-CETP Co Operative Society Ltd. (7.5)	No
				RIA CETP Co-op. Society Ltd. (22.5)	No

Note: ^These CETPs are in Solapur. (-) denotes no CETP in the region; NA is not applicable

State	Hub location/ district/ region	Hub largely manufacturing (API/FPP/API and FPP)	No. of CETP(s)	Company managing CETP (capacity in MLD)	Waste water recovery system
Gujarat	Baruch, Dahej	API	1	CETP of Dahej Industrial Estate (40; 5-6 operational)	No
	Baruch, Ankleshwar	API	3	Enviro Technology Ltd. (3.5)	No
				Narmada Clean Tech Ltd. (40)	No
				Panoli Envirotech Ltd. (1.1)	No
	Valsad, Vapi	API	1	Vapi Green Enviro Ltd. (55)	No
	Vadodra	API and FPP	2	Nandesari Industrial Association (12)	No
				Enviro Infrastructure Co. Ltd. (4.5)	No
	Ahmedabad	API and FPP	5**	Zydus infrastructure Pvt Ltd (4.5)	Yes
				Naroda Enviro Project Ltd (14)	No
				Odhav Enviro Project Ltd. (1.2)	No
				Gujarat Vepari Maha Mandal Sahkari Udhyogik Vasahat Ltd (0.45)	No
				The Green Environment Services Co. Op. Society Ltd (16)	Yes
Karnataka	Bidar, Kolhar industrial area	API	1	Mother Earth Environ Tech Pvt Ltd. (0.5)	Yes
	Raichur	API	-	NA	NA
Goa	South Goa Verna	FPP	-	NA	NA
Sikkim	Pakyong district, Rangpo- Rorathang area	FPP	-	NA	NA
	Namchi district, Samardung area	FPP	-	NA	NA

Source: Based on information received/collected from RTI responses, websites of state pollution control boards, discussions with SPCB officials, and secondary research. Information is non-exhaustive.

**In Ahmedabad, there are 11 operational CETPs, out of which six are not receiving waste from pharmaceutical companies, therefore only five were considered. (-) denotes no CETP in the region; NA is not applicable

5.3. CETP inlet and outlet standards

As per CPCB categorization of industries, the CETPs are also placed under red category, but they come under special category projects as these are part of pollution control facilities. For CETP, the categorization also depends upon the category of member industries being served. CETPs are required to carry out online continuous effluent quality and emission monitoring.[75]

The Environment (Protection) Amendment Rules, 2015 provides quality standards for the treated effluent leaving the CETP and disposed into three different areas.[76] These are—inland surface water, land for irrigation and into the sea. Standards for general and specific parameters are separately provided for these three areas (unlike the effluent standards for the pharmaceutical industry). The general parameters include pH, BOD, COD, TSS, fixed dissolved solids (FDS) while specific parameters include temperature, oil and grease, ammoniacal nitrogen, Kjeldahl's nitrogen, several heavy metals and Bio-assay test *(see Table 10: Treated effluent quality standards for CETPs)*. It is noteworthy, that there are no standards for residual antibiotics in treated effluents released from CETPs. The limiting values for antibiotic residues as per draft 2020 MoEFCC standards were applicable for CETPs in addition to industry's ETP.

For the inlet effluent, the standard mentions that for each CETP, the SPCB shall prescribe inlet quality standards for general parameters, ammoniacal nitrogen and heavy metals as per the design of the CETP and local needs and conditions. It is clear that inlet effluent quality standards have either been prescribed by states as a common standard applicable to all CETPs in the state (e.g., Maharashtra,[77] Delhi[78]) or separately for each CETP in the state (e.g., Haryana,[79] Karnataka,[80] Uttarakhand[81]). In case of the latter, the standard values for a single parameter may also vary from one CETP to another.

Table 10: Treated effluent quality standards for CETPs

Parameter	Standards		
	Max. permissible values (in mg/l except for pH and Temperature)		
	Into inland surface water	On land for irrigation	Into sea
General parameters			
pH	6.0-9.0	6.0-9.0	6.0-9.0
Biological Oxygen Demand (BOD, 3 days, 27°C, mg/l)	30	100	100
Chemical Oxygen Demand (COD, mg/l)	250	250	250
Total Suspended Solids (TSS, mg/l)	100	100	100
Fixed Dissolved Solids (FDS, mg/l)	2100	2100	NS
Specific parameters			
Temperature,°C	Shall not exceed more than 5°C above ambient water temperature	Shall not exceed more than 5°C above ambient water temperature	Shall not exceed more than 5°C above ambient water temperature
Oil & grease	10	10	10
Ammonical-Nitrogen	50	NS	50
Total Kjeldahl Nitrogen (TKN)	50	NS	50
Nitrate-Nitrogen	10	NS	50

Parameter	Standards		
	Max. permissible values (in mg/l except for pH and Temperature)		
	Into inland surface water	On land for irrigation	Into sea
Phosphates, as P	5	NS	NS
Chlorides	1,000	1,000	NS
Sulphates, as S04	1,000	1,000	NS
Flouride	2	2	15
Sulphides, as S	2	2	5
Phenolic compounds (as C_6H_5OH)	1	1	5
Total Residual Chlorine	1	1	1
Zinc	5	15	15
Iron	3	3	3
Copper	3	3	3
Trivalent chromium	2	2	2
Manganese	2	NS	2
Nickel	3	NS	3
Arsenic	0.2	NS	0.2
Cyanide, as CN	0.2	NS	0.2
Vanedium	0.2	NS	0.2
Lead	0.1	NS	0.1
Hexavalent chromium	0.1	NS	0.1
Selenium	0.05	NS	0.05
Cadmium	0.05	NS	0.05
Mercury	0.01	NS	0.01
Bio-assay test	As per industry specific standards	As per industry specific standards	As per industry specific standards

Notes: NS-Not specified.

Detailed notes on these rules can be found here:
https://cpcb.nic.in/displaypdf.php?id=SW5kdXN0cnktU3BlY2lmaWMtU3RhbmRhcmRzL0VmZmx1ZW50L0NFVFAucGRm

Bold text indicates sector specific parameters for the pharmaceutical industry sector.

Source: Environment (Protection) Amendment Rules, 2015

5.4 Case studies—CETPs

Two CETPs were selected for detailed study. One is the Baddi CETP, located in Baddi-Barotiwala-Nalagarh (BBN) area of Himachal Pradesh which is a formulation producing hub. The reason for selecting this CETP is that it is relatively new, and it lies in a region which has recently been under scrutiny by central and state pollution control regulators

as well as the NGT for causing antibiotic pollution due to improper waste management by pharmaceutical manufactures.[82] The other CETP selected is the Jeedimetla Effluent Treatment Limited (JETL), located in Hyderabad in the state of Telangana which largely caters API producers. This is one of the oldest functioning CETP in the country. Moreover, pharmaceutical pollution has been a concern in the region for many decades.

A. CETP of Baddi, Himachal Pradesh

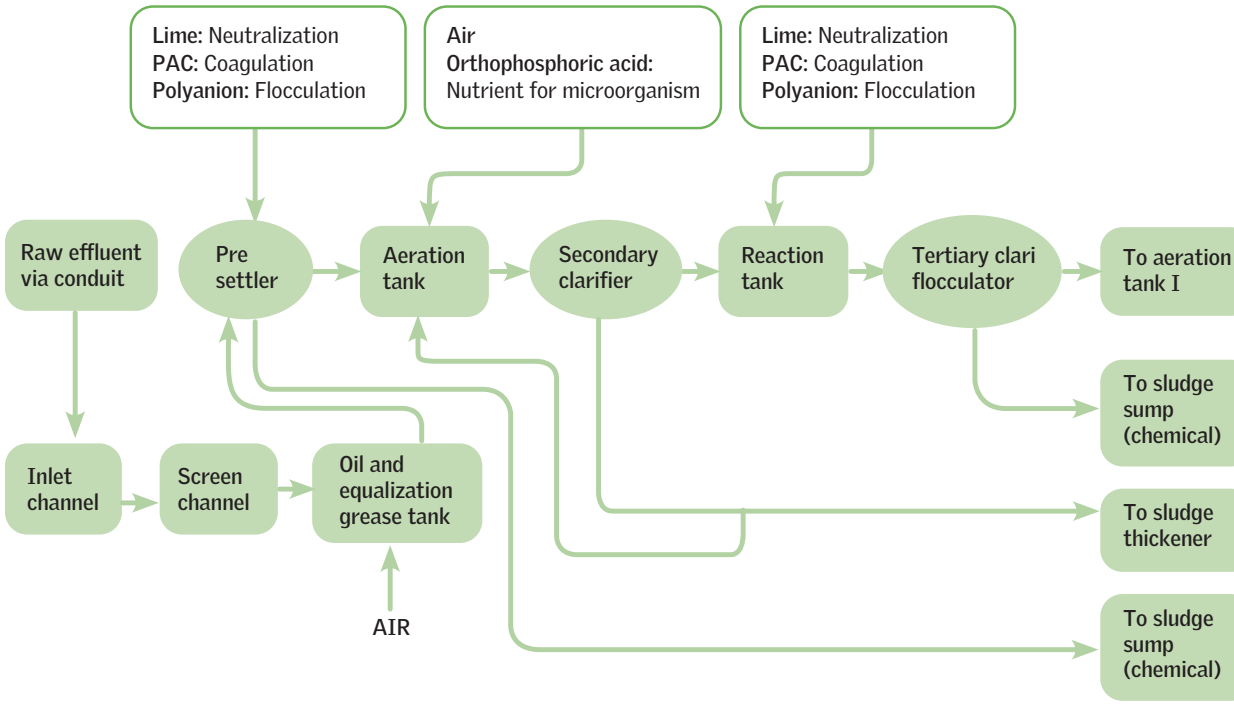
Baddi, Barotiwala, an industrial belt of district Solan in Himachal Pradesh is home to many industries like textile, dye, pharmaceutical among others. Rapid industrialization happened in this region as a result of the special industrial packages of incentives granted by the government of India in 2003. By 2009–10, Baddi, was declared as a severely polluted area by the CPCB.[83] The High Court of Himachal Pradesh via case no. CWPIL 13/2006, suggested to set up a Common Effluent Treatment Plant for Baddi and Barotiwala area. The project was to be handled by Baddi Infrastructure.[84] Based on the secondary and primary data related to industries, capacity of the CETP was designed for 25 MLD *(see Box: Waste management practices in Baddi pharmaceutical hub as observed in 2017).*

The CETP receives effluents from five types of industries - textile, soap and detergent, dye, electroplating, and pharmaceutical industries. More than 400 units are connected through tankers and pipelines, out of which about 240 are pharmaceutical companies largely manufacturing FPPs. Eighty per cent of the incoming effluent is from textile industry and the contribution of the pharmaceutical industries is approximately 2.5 MLD. The treatment approach deployed at the CETP is to separate all five streams of effluents and treat them

WASTE MANAGEMENT PRACTICES IN BADDI PHARMACEUTICAL HUB AS OBSERVED IN 2017

In 2017, CSE researchers had travelled to Baddi, Himachal Pradesh to understand waste management practices followed by pharmaceutical units in the BBN area.[85] Interaction with stakeholders as well as observations made from different site visits suggested improper disposal of pharmaceutical industry waste. For example, waste pickers mentioned that solid waste from the industry was given to scrap dealers who would discard or burn them in any open area. Researchers, with the help of locals, also visited one such place where medicinal waste had been recently burnt, and liquid chemical waste drained. According to locals, effluents were being injected into bore wells dug in the ground at night. The ETPs also released toxic effluents during monsoon, while smaller companies drained their ETP treated water into nallahs. Officials from the State Pollution Control Board, on condition of anonymity, also indicated that the sewer lines of some industries are not connected to CETP and open directly into the nearby river. Upon visiting the external boundaries of some manufacturing plants along with locals, CSE researchers found that pipes/outlets from manufacturing plants opened at the backside of the plant, or were being channelled underground to open into bushy, low-lying areas. In some cases, the manufacturing wastewater was passed underground to drain out at a different area, away from the vicinity of the plant. CSE researchers also visited the Sarsa river, into which treated effluents from the then newly constructed CETP (situated at the village Kenduwal in Baddi) were being released. Brown/black coloured effluents were seen flowing through it, and the area around the river was also stinking.

Figure 5: Schematic representation of the working of the Baddi CETP, Himachal Pradesh



separately and subsequently mix them after individual treatment before final discharge *(see Figure 5: Schematic representation of the working of the Baddi CETP, Himachal Pradesh).*

Post screening of the raw effluent, all incoming pharmaceutical effluent, irrespective of the company, is mixed together in the equalization tank for homogenization. From there, the effluent is sent to the pre-settler which reduces the Total Suspended Solids (TSS) and Suspended Solids (SS). In order to reduce the load, chemicals like lime, polyanions and polyaluminium chloride (PAC) are added in the pre-settler through a venturi system.

The overflow from the pre-settler is sent to the aeration tank, which has microorganisms that act on the organic matter, lowering the BOD/COD levels. The overflow from the aeration tank is then sent for clarification to the secondary clarifier. Some of the sludge from this tank is recovered (as it has microorganism) and sent back to the aeration tank (as inoculum). The overflow from the secondary clarifier is sent to the reaction tank where the chemicals like lime, polyanions and polyaluminium chloride help with the flocculation and coagulation. This step again helps in reducing the BOD/COD levels. Finally, the overflow from the reaction tank is sent for clarification in the tertiary clari-flocculator.

The overflow from the tertiary clari-flocculator is sent to join the category I (textile) effluent and treated once again as the outlet quality does not meet the required CETP outlet standards here. In parallel, the sludge formed by clarification from the pre-settler, secondary clarifier and tertiary clari-flocculator is sent for collection and then sent to a transport storage disposal facility (TSDF) facility for disposal.

Once treated, all effluents from the five categories are mixed, forming one stream that is discharged through the final outlet. Data regarding the basic parameters, i.e. BOD, COD, TSS, pH, are shared with the SPCB and the CPCB through a real-time monitoring system.

Regarding the treatment of wastewater, a company enters into a agreement with Baddi Infrastructure, CETP, SPCB. In terms of payments involved, an internal formula is used by the CETP which decides the cost per KL of every incoming tanker. This formula takes into account parameters such as BOD, COD, TSS and total dissolved solids (TDS). At the end of the specified period of time (e.g., week/fortnight/month), a consolidated bill is generated and sent to the particular for payments. For a pharmaceutical company that sends its wastewater to the CETP, the cost per tanker (capacity 10 KL) could be about Rs 1,000-2,000. This is about Rs 100–200 per KL.

B. Jeedimetla Effluent Treatment Limited (JETL), Telangana

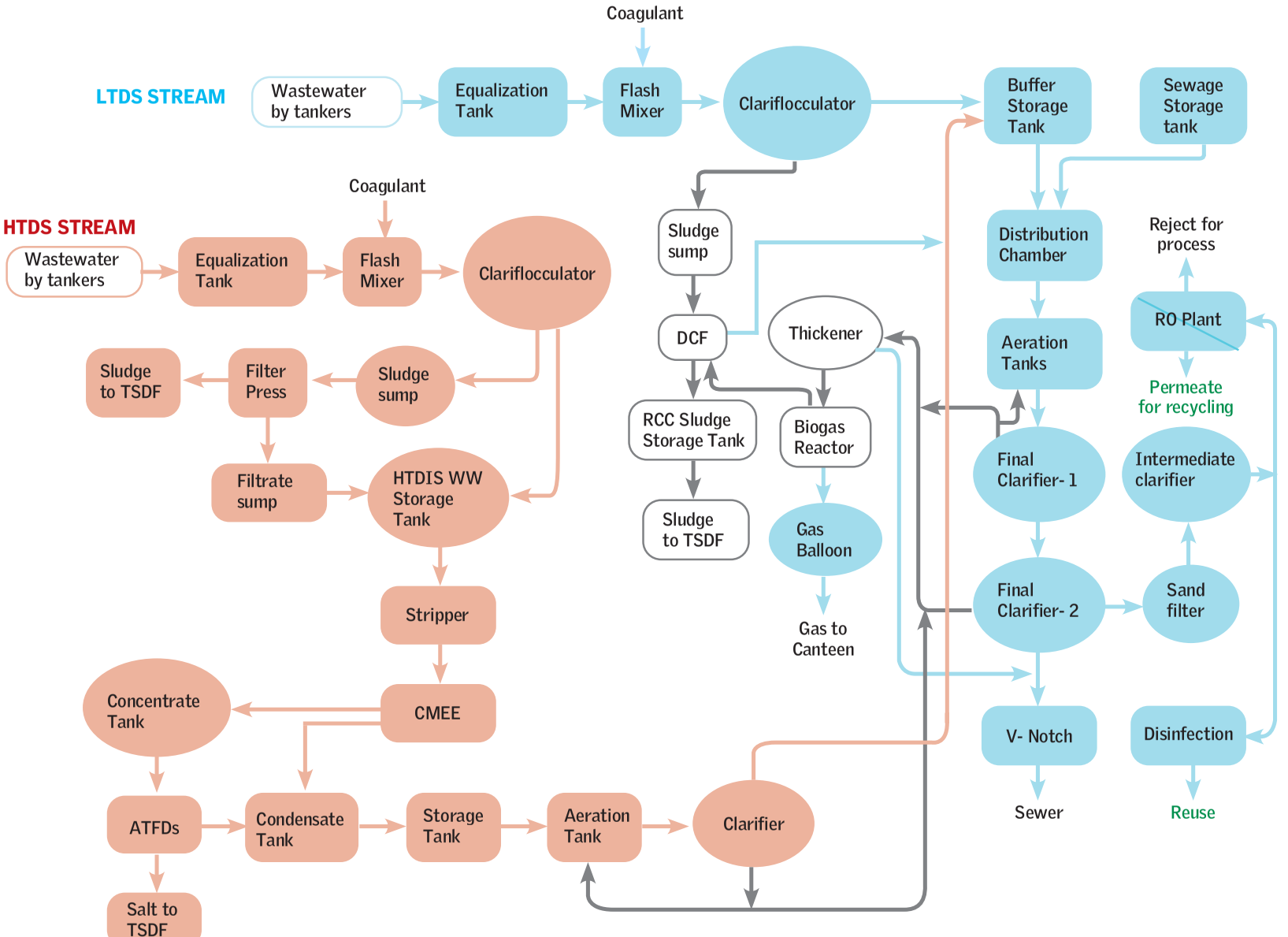
One of the earliest pharmaceutical industrialization in India began in the Patancheru-Bollaram Industrial cluster of Telangana in the 1970s. Due to the lack of stringent environment regulations, the effluents from pharmaceutical industries were being discharged into water bodies directly or indirectly, with effluents even percolating to the ground water and agricultural fields.[86] Multiple petitions have been filed since in Indian courts by civilians, organizations etc. regarding this growing pollution. In response to petitions and public concerns, several interim orders have been passed by Indian courts, including the creation of a special task force in the Telangana SPCB, the development of a joint action plan, etc.

The Jeedimetla Effluent Treatment Ltd. (JETL) started their operation in 1989 as a CETP to cater to the needs of waste management by small and medium industries in Hyderabad. In 1998, the CETP was converted into a Combined Wastewater Treatment Plant (CWWTP) for treating industrial waste and the domestic sewage in a combined plant.[87]

It has a capacity of five MLD and is located in the Medchal district of Hyderabad, Telangana. It caters to 350 companies, 70 per cent of which are pharmaceutical units. The rest of the companies belong to dye, dairy, electroplating and chemical sectors, as well as household sewage stream *(see Figure 6: Schematic representation of the working of Jeedimetla Effluent Treatment Limited, Telangana).*

The facility is said to be a partial ZLD facility because their RO system does not have 100 per cent efficiency. It has a different approach than the Baddi CETP. The incoming effluents from companies are differentiated on the basis of TDS. Broadly, the effluent streams containing higher TDS are passed through MEE. The water is evaporated and leaves with concentrated inorganic salts containing still higher TDS. The evaporated water is condensed and the condensate goes to join the low TDS stream after the biological treatment. The concentrated salts are either directly incinerated or passed onto the ATFD for further drying. Again, evaporated water from the ATFD is condensed and fed into biological treatment

Figure 6: Schematic representation of the working of Jeedimetla Effluent Treatment Limited, Telangana



Abbreviations: LTDS-Low Total Dissolved Solids; HTDS-High Total Dissolved Solids; CMEE-Common Multiple Effect Evaporator; TSDF-Treatment Storage and Disposal Facility for Hazardous Waste; DCF-Decanter Centrifuge; ATFD-Agitated Thin Film Dryer; HTDIS WW-High Total Dissolved Inorganic Salts Wastewater; RCC-Reinforced Cement Concrete; RO- Reverse Osmosis

Note: Red boxes and arrows depict High TDS stream; Blue boxes and arrows depict Low TDS stream

tanks. Sometimes, very high TDS streams are fed directly into ATFD. Solid residues from the MEE or ATFD residue is disposed at an approved TSDF site.

The low TDS stream undergoes pre-treatment for silica removal, before it goes to treatment in RO. The water from the RO generates permeate (treated water) and RO reject. Permeate from RO goes to the boiler or for secondary use, while the RO reject is passed onto the MEE.

100 per cent of the high TDS effluent is said to be coming from the pharmaceutical industry (which is approximately 300 KLD), while about 60 per cent of the low TDS effluent is contributed by pharmaceutical industries.

Online monitoring is reportedly being done and physical sample collection is done daily for JETL outlet to check for basic parameters (like BOD, COD, TDS, TSS, pH).

Units generating >25 KLD effluent are not allowed to be sent to the JETL and have to make their own treatment arrangements. For the ones who are eligible to send their effluents to the JETL, an agreement is made between the JETL and company, on the basis of parameters like TDS and COD, pH. The rates are decided per 10 KL. The cost determination is done separately for low and high TDS effluent irrespective of the industry from which the effluent is received. On an average, for low TDS effluents the cost of treatment comes in the range of Rs 170–230 per KL and for high TDS effluents the cost of treatment comes in the range of Rs 2000–6000 per KL. The costing details of Jeedimetla Effluent Treatment Limited can be seen in Annexure 7.

Understanding from the two CETP case studies

The Baddi CETP and JETL, Telangana show two different approaches of wastewater management being used. While Baddi CETP segregates wastewater based on the type of industry and treats it separately, JETL distributes waste streams irrespective of industry into high and low TDS and treats it according to the TDS. The type of effluent received by Baddi CETP is likely to have a lower TDS since it caters to formulation producers, while in case of JETL, the effluents being received can have both high and low TDS owing to API manufacturers dominating the region.

The JETL has modified its infrastructure to include MEE, ATFD and RO, such that it can now operate as a zero liquid discharge (ZLD) facility and treat high and low TDS effluents. Baddi CETP, on the other hand, does not have such facilities, but uses a cost-effective approach for treating the pharmaceutical effluent twice.

The costing approach is also different for the two. Baddi CETP takes into account an internal formula to decide on the cost per KL. Since the formula depends on parameters like BOD, COD etc. the cost would differ from industry to industry based on the quality of the effluent being sent. In case of JETL, the costing is based on standardized values of TDS (different for low as well high TDS effluents) and COD.

6. Approaches to reduce antibiotics in wastewater

A mixture of process control and waste management approaches are being used by the industry as part of their manufacturing processes, to limit the passage of antibiotics into the environment through waste. The selection of waste management technologies depends on several factors and may vary depending on utility, cost and feasibility of implementation. This chapter discusses such measures and technologies.

6.1. Process control measures

Appropriate control at the process level can significantly help reduce the load of antibiotic APIs entering a plant's wastewater effluent, without going for expensive end-of-pipe treatments or applying an expensive technology at the wastewater treatment plants. Some examples of the process control measures are:

a. **Mass balance approach** can aid with identifying wastewater stream(s) that could be segregated for disposal at an off-site facility, that are suitable for effective on-site treatment prior to disposal, and those that will require specific pre-treatment prior to disposal to a wastewater treatment system.
b. **Equipment cleaning procedures** can be optimized to reduce the API loading and to lower disposal costs by
   (i) Performing initial dry cleaning and by reducing the volume of high-strength rinses being generated (done before wet cleaning).
   (ii) Capturing the first rinse of the equipment. An additional separate cleaning step (pre-rinsing) can remove large portions of APIs from large-volume wash waters. The high-load pre-rinse streams can be separated and addressed subsequently by a selective technology or incineration/thermal oxidation. This limits high concentration of APIs from going into the waste stream.
c. **Spill control** during production process is contained and cleaned up appropriately.

6.2. Wastewater treatment technologies

A. Deactivation of beta-lactam antibiotic by strong alkali

One of the cost-effective approaches claimed to be used by some of the small- and medium-scale industries when it comes to the management of wastewater is deactivation of beta lactam antibiotic by strong alkali. The wastewater, before being discarded or primary treated is subjected to treatment under high pH, using alkaline agents such as sodium hydroxide (NaOH), sodium hypochlorite (NaOCl) or hydroxyl amine (NH_2OH) for few hours. For example, in the case of NaOH, nucleophilic attack of OH- ion on the ring takes place. This alkaline hydrolytic reaction leads to immediate beta-lactam ring opening and degradation

towards inactive derivatives, and subsequently towards a variety of further degradation products, all inactive against bacteria due to the missing key beta-lactam moiety.[88]

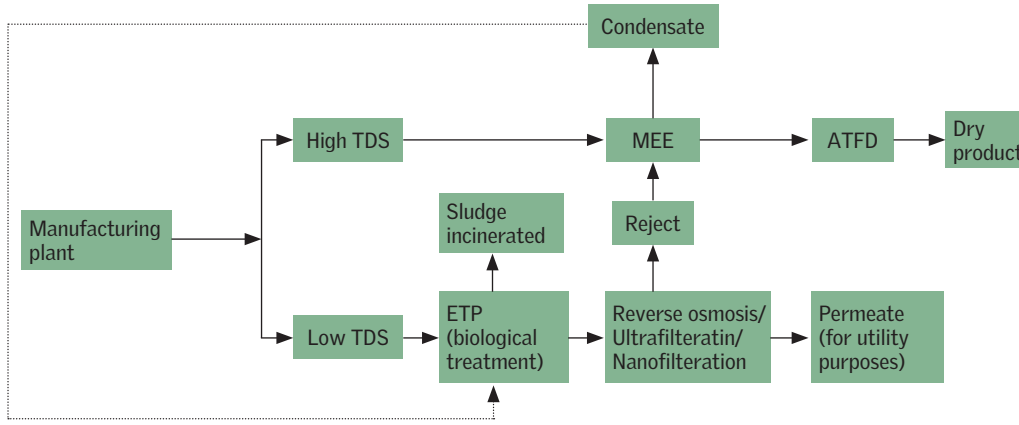
Using the deactivation approach is economically viable. The cost per kg of sodium hydroxide is around few hundred rupees. For a medium-sized formulation company generating around 10 KLD effluent, 5–10 kgs of NaOH is required daily, which can cost around Rs 1,000. The method is quite cheap and requires minimal infrastructure. This includes a container of appropriate size to hold the effluent along with the deactivating agent (NaOH) for a suitable amount of time for the reaction to occur. The container should however be able to resist corrosive action by the alkali.

B. Zero Liquid Discharge approach

Another approach of wastewater management is the use of Zero Liquid Discharge (ZLD). This is largely cited by large-scale manufacturers of antibiotics. It is an approach to reduce volume of wastewater being discharged.

The ZLD approach involves the use of facilities and systems that enable absolute recycling of or reuse of industrial effluent, and converting the solute (dissolved organic and in-organic compounds/salts) into solid form through concentration and evaporation.[89] It is aimed to minimize the volume of wastewater at source, which would otherwise need treatment. ZLD provides an economically feasible wastewater recycling and reuse approach *(see Figure 7: Schematic representation of ZLD system operation).*

Figure 7: Schematic representation of ZLD system operation



The effluent is first segregated into two streams based on low and high TDS content. The low TDS effluent stream is sent directly for biological treatment in the ETP, from where the sludge is removed and incinerated. The treated water is further subjected to reverse osmosis/ultrafiltration/nanofiltration. For example, the water from the RO generates permeate (treated water) and RO reject. The permeates can be reused in cooling towers and scrubbers within the plant, while the RO reject is passed onto the MEE which evaporates it.

The effluent streams containing higher TDS are passed through MEE. The water evaporates and leaves with concentrated inorganic salts containing still higher TDS. The evaporated water is condensed and the condensate is further fed into the biological treatment tank within the ETP. The concentrated salts are either directly incinerated or passed onto the ATFD for further drying. Again, evaporated water from the AFTD is condensed and fed into biological treatment tanks. Sometimes, very high TDS streams are fed directly into the ATFD. Solid residues from the MEE or ATFD residue is disposed at an approved TSDF site. The permeate generated in a ZLD system can be utilized within the industry premises, such as in cooling towers, boilers or at times in gardening/horticulture.

At times, companies establish only MEE or only ATFD, instead of the complete ZLD system. Both MEE and ATFD are largely aimed for water recovery and do not generate any outlet effluent. MEE uses the heat from steam to evaporate water. Water is boiled in a sequence of vessels, each of which is at a lower pressure than the last.[90] Although suitable for high TDS effluents and in large scale continuous operations, the use of MEE is not energy efficient owing to the high energy consumed. Also, the condensate released can contain high levels of pollutants. The ATFD, as the name suggests, is a dryer used to produce dry powder from slurry/solution, in situations where the solutions cannot be handled by conventional dryers/evaporators. It usually follows MEE. It is energy-intensive and suitable for high TDS effluents. It also costs more than a standard evaporation equipment.

However, before subjecting the effluent to ZLD, it should undergo physical, chemical and biological treatment to remove organic load.

The cost of a ZLD plant can also depend on the type of industry (API/ formulation), scale of industry (small/medium/large), and outlet parameters of the effluent required. For example, for a medium-sized formulation unit generating 10 KLD effluent, ZLD can cost around Rs 50 lakhs, with a maintenance cost of around Rs 5–10 lakhs annually. Similarly, for a medium-scale API/intermediate manufacturer, generating around 30 KLD effluent, the cost of establishing ZLD can be around Rs 5–6 crore. Maintenance could be about Rs 15–20 lakhs annually.

According to the Indicative Guidelines on 'Techno—Economic Feasibility of Implementation of Zero Liquid Discharge (ZLD) for Water Polluting Industries,' published by the CPCB in 2014, the cost of a combination of conventional ETP with ZLD facilities can be about Rs 12.0 to 15.0 crores per MLD.[91] This is much higher than the cost of a CETP treating 1 MLD of wastewater with conventional physico-chemical and biological treatment which is around Rs. 3 to 4.0 crores along with operation and maintenance cost of Rs 300–350 per cubic meter (m^3).

C. Advanced wastewater treatment technologies

In addition, there are also some advanced technologies of wastewater treatment, which are emerging as potential options to remove specific compounds like antibiotics.

This is because conventional treatment technologies such as neutralization, equalization and biological treatment technologies for wastewater treatment are often not able to remove antibiotic residues from wastewater.

- **Advanced biological processes** such as membrane bioreactors involve the use of a microfiltration membrane to separate the solids from the liquid. The membrane bioreactors can degrade organic compounds that require a long contact time and acclimation period.[92]
- **Membrane processes** can be effective for large molecule separation. They generate a concentrated liquid waste for disposal or further treatment and can be effective when installed near the source to reduce the amounts of APIs going to treatment processes downstream.
- **Activated carbon adsorption method** commonly uses granular or powdered activated carbon to adsorb natural and synthetic organic compounds from wastewater (via hydrophobic interaction with activated carbon surface). In certain applications, it can be an effective treatment technology due to the highly porous nature and large surface area to which contaminants may adsorb onto the media.
- **Advanced oxidation processes** (**AOPs**) use chemicals to generate hydroxyl radicals (•OH), which oxidize antibiotic molecules in wastewater into smaller organic molecules through chemical oxidation process (e.g., ozone, Fenton's reagent, chlorine, UV light, ozone combined with hydrogen peroxide (O_3/H_2O_2) and ultraviolet light combined with hydrogen peroxide (UV/H_2O_2)[93] *(See Annexure 8: Assessment of select advanced wastewater treatment technologies).*

A review of recent literature has shown that these technologies have been quite efficient in degrading antibiotics present in pharmaceutical wastewater samples *(see Annexure 9: Antibiotic degradation in pharmaceutical wastewater with advanced wastewater treatment technologies).*

Laboratory-based studies on real or synthetic/artificial/simulated pharmaceutical wastewater have shown that technologies such as AOPs, membrane bioreactors and activated charcoal adsorption have been able to degrade antibiotics in the range of 30–100 per cent. A large number of the studies have opted for the use of AOPs such as photocatalysis, photo-fenton oxidation and ozonation methods which have shown antibiotic degradability within the range of 95–100 per cent. The use of AOPs have shown degradation of antibiotics belonging to different classes, such as fluoroquinolones (e.g., levofloxacin, ciprofloxacin), penicillins (ampicillin, oxacillin), cephalosporins (e.g., ceftriaxone). Membrane bioreactors have also shown good degradability of β-lactam antibiotics, as well as antibiotics belonging to classes—fluoroquinolones, macrolides, sulfonamides, and tetracyclines.

7. Way forward

A. It is clear that:

1. **Consensus to act on manufacturing discharge is growing** among the global scientific community and governance structures. There is a recognition that despite certain gaps, the current level of evidence is enough to act and contain antibiotic manufacturing discharge due to silent AMR crisis.
2. **AMR Industry Alliance response is in the right direction but lacks scale**. It is a measured response that encourages voluntary adoption of agreed-upon measures among a limited set of companies. But to be substantially effective, it needs to be adopted at a wider level by the big global industry and at a deeper level, among their supplier networks.
3. **Huge expectations from the Indian pharmaceutical industry** to contain antibiotics in manufacturing discharge. The Indian industry is an integral part of the global antibiotic supply chain and provides generic antibiotics to several countries, both high-income and low-and-middle-income countries.
4. **No standards to directly address antibiotics in manufacturing discharge.** While the Indian policy framework considers the pharmaceutical industry (particularly API manufacturing) as the one with a high pollution-causing potential, the legal standards set for compliance do not address the issue of pollution due to antibiotic residues.
5. **The antibiotic limits proposed in the draft Indian standard are based on science.** Just as the Predicted No Effect Concentration (PNEC) targets adopted and endorsed by the AMR Industry Alliance, the proposed antibiotic limits are based on the same set of PNEC values published by a group of scientists. One key difference is that the proposed limits also incorporate reduction efficiencies of the ETP/CETP. Therefore, these are atleast 60 per cent lower than PNEC targets in most cases and are to be applicable at the treated effluent of bulk drug and formulation industry, and CETPs with membership of bulk drug and formulation units and not at receiving water body, at which PNEC targets are applicable.
6. **Pharmaceutical companies adopt a varying set of waste management approaches based on several factors.** Most large-scale companies claim to also focus on process control measures to minimize the entry of antibiotics into the waste stream along with waste management approaches that rely on technologies supporting ZLD, and a few advanced technologies if need be. On the other hand, small-and medium-scale manufacturers prefer a limited set of cost-effective approaches for in-house treatment at ETP and rely on CETPs for final treatment.
7. **Most CETPs in antibiotic hubs rely on conventional treatment approaches** and often lack advanced treatment or wastewater recovery systems. While there are examples of customized practices at CETPs which appear to be effective, their role becomes critical considering that a large number of small and medium companies manufacturing APIs and FPPs rely on CETPs.

8. **There is clear evidence that antibiotic pollution is a reality.** Antibiotics have been detected in effluent samples of several companies as well as CETPs. This means that waste management approaches claimed to be followed by the industry in general does not guarantee safe discharge. The process control measures have a critical role to play as do effective pollution control technologies.
9. **Waste management approaches are best when adopted based on specific factors of a company/CETP.** There are technologies that can reduce antibiotics to a considerable extent but each has its own advantages and disadvantages, which could vary based on the size and nature of the manufacturing company**.**

B. Why action is needed:

- **Action on antibiotics in manufacturing discharge can be very effective.** It is important to recognize that antibiotics in manufacturing discharge is one of the many known driver of the AMR crisis. Just like the pharmaceutical sector, AMR routes from all othe sectors like human-health, food, animals and crops need to be addressed with similar priority. This also means that pharmaceutical sector should not get de-prioritized. In fact, action on manufacturing discharges is relatively less complicated compared to other sectors due to the localized presence of antibiotics at high concentration and limited set of known stakeholders who have the capacity to reduce the problem and are also resourceful. It is an important hotspot more from the perspective of possibility for effective action.
- **Effective action is linked to several challenges, which need to be systematically addressed.** Among the few big challenges often referred to is the challenge of maintaining antibiotic supply chains and the challenge of access to cheap antibiotics. This understanding is rooted in the premise that reducing antibiotics in discharges will incur huge costs for the manufacturing companies. While this is true and more so for the large number of small-and medium-scale antibiotic manufacturers, but it is also important to compare this with overall cost burden of AMR. Moreover, the cost for effective action will have to be shared as all stakeholders including the government should come together to systematically address this issue, for e.g, in the case of upgrading CETPs .
- **India's pharmaceutical industry stands to gain in the long-term, if it timely initiates and supports effective action.** India is a big producer and exporter of antibiotics. Considering the growing global momentum to procure antibiotics manufactured sustainably, the pressure to supply such antibiotics may eventually start affecting India's big antibiotic exports sector. Another significant reason to act is the link between antibiotics in discharge and their long-term value/usefulness at the national and global level. More antibiotics in discharge means more in environment that can cause more resistance making more antibiotics ineffective. Containing antibiotics in discharge is also cited as a big reason to keep antibiotics working since not many new antibiotics have been developed over the last several decades and as the pipeline is also not promising. This is seen as an important measure to preserve the existing ones for long-term use.
- **India will be hugely benefitted from an effective action. This can be an opportunity to invest in preventing the potential future health and economic crisis.** Infectious

diseases are a big cause of health and cost burden, particularly among the large poor population of the country. Antibiotics are no less than magic bullets. They save lives. They also save livelihood of many as India has a big poultry, dairy, fisheries sector. With Covid-19 pandemic, countries have also seen the importance of having effective medicines/ vaccines. Absence of effective antibiotics is a development concern. India cannot afford the rising crisis of antibiotic resistance and therefore should take this as an opportunity to do everything that can be done to prevent this potential crisis. We know the importance of prevention. We know that prevention is better than cure.

C. What needs to be done:

National and state government ministries/departments/regulatory agencies/scientific and academic institutes:

1. **Invest in creating awareness and building capacity among stakeholders:** The first and foremost effort should be to create necessary awareness as well as build relevant capacity among the different sets of stakeholders involved, such as the state pollution control boards, and antibiotic manufacturing industry. Efforts should be focused on generating awareness on basic areas such as AMR, its drivers, impacts, different contributing pathways; different AMR causing determinants and ways to reduce their entry into environmental pathways, particularly through the pharmaceutical manufacturing effluent; different approaches of process control and waste management, including the use of new technologies, and importance of documentation, reporting and data sharing. Necessary capacity among stakeholders should be built in parallel.

2. **Data development to support policy formulation, implementation and monitoring:** All necessary basic-level national and state-level data should be collected and consolidated to support the required policy formulation and implementation. This can be done through a coordinated initiative between the Central and State Pollution Control Boards, Central and State Drug Control Departments and Department of Pharmaceuticals. Currently, the data available is limited and sporadic, and needs to be put together and updated periodically. Such an exercise should aim to develop an understanding on:

- Identifying who the manufacturers of antibiotics are and their locations
- Identifying the kind of antibiotics being manufactured and their quantities
- The quantity of wastewater generated and the kind of waste management approaches/ technologies that are in use; the treatment followed at in-house ETPs
- The capacities and capabilities of CETPs; their locations and connectivity with manufacturing units

3. **Formulate and implement a long-term research agenda:** The need for more evidence on different aspects should be addressed through a concerted national-level research programme. Initiated by the governments' scientific departments/academic institutes, such as departments of science and technology as well as biotechnology, such a programme is best if based on an open platform/sourcing that encourages and recognizes

research by a wide set of stakeholders, including the pharmaceutical industry. This programme should consider developing a better understanding on:

- The relationship between the concentration of different antibiotics, resistance genes and development and spread of resistance, based on the field data
- The persistence and presence of different antibiotics across possible routes, including food chain; and their ecological/eco-toxic impact
- The limiting values for antibiotic resistance genes, if any and the role of genomic surveillance
- The development of low-cost and effective waste management technologies/approaches to treat different antibiotics in view of small-and medium-scale antibiotic manufacturers and CETPs
- Validated test methods for all antibiotics; low-cost kits for testing antibiotics in environmental samples

4. **Regular surveillance and monitoring of manufacturing units and CETPs:** SPCBs, with help from CPCB, should conduct regular surveillance and monitoring of manufacturing units and CETPs with regard to antibiotics in effluents. CPCB Guidelines on the Monitoring Mechanism for API residues should be referred. Notably, it is the State Pollution Control Boards who have a key role in surveillance and monitoring, because of their vicinity and greater awareness of the practices being followed in the state. Such data should be available in the public domain and be aimed to develop an understanding of the following:

- Detect levels of antibiotics in samples from the ETP of manufacturing unit and CETPs
- Inspect and ensure that wastewater is not discharged unlawfully without treatment
- Check if the desired segregation and process control measures are followed to minimize the entry of antibiotics in wastewater, and reduce wastewater quantity
- Conduct audits on the documentation on waste stream analysis, mass balance etc.

5. **Strengthening laboratory capacity to support surveillance efforts:** In order to facilitate routine surveillance and the monitoring of manufacturing units and CETPs, it is equally important to strengthen current laboratory capacity. This includes improving laboratory infrastructure at the state-level with the necessary equipment for detection of antibiotic residues, developing necessary standard operating procedures, validating methods etc.

6. **Notify legal limits for antibiotics in discharge from manufacturing units and CETPs:** Just like limits are set for other hazardous toxic chemicals and heavy metals in pharmaceutical and CETP discharges, antibiotics should have a legal limit which polluting entities can adhere to and regulatory agencies can refer to while checking for compliance. Unregulated discharge from antibiotics poses a big threat to the existence of humanity and aquatic ecosystem.

One option is that MoEFCC notifies the limiting values it proposed in its draft of 2020. But, if these are considered too stringent, the PNEC targets developed by the pharmaceutical industry itself can be considered to begin with. Considered feasible to test and achieve, these targets are also accepted largely among the global scientific community, which makes them suitable for a harmonized approach that can facilitate international trade/supply of antibiotics in the future.

But these targets should be applied to the treated effluent from the manufacturing units' ETP and CETPs connected to it, instead of receiving water body. There are several reasons for this. Application of the standards at the receiving water body means relying on the assimilative capacity of the receiving body, which could vary due to multiple reasons including season and location. But as assimilative capacity itself is dependent on the aquatic ecosystem and antibiotic residues from discharge can kill the bacteria and negatively impact the biotic component of the aquatic ecosystem, the concept of assimilative capacity cannot be applied here. Monitoring at receiving water body will further make it difficult to attribute an increased residue level to the actual defaulter, thereby creating enforcement hurdles and absence of incentives/disincentives for the manufacturer. Standards should therefore be applied at end of the pipe i.e. at the ETP outlet of the manufacturing unit and the outlet of CETP connected to it.

7. **Upgrade and enable capacity and capability of CETPs to address antibiotics:** Several antibiotics have been found at very high levels in discharges from CETPs. Considering that a large number of small-and medium-scale manufacturing units rely on CETPs for final treatment, it is of critical importance that all such units across the country are appropriately connected to CETPs. The assessment of CETPs is done to identify gaps, based on which their capacity and capability is enhanced to degrade antibiotic residues so that antibiotic discharge in the environment is minimized. If limiting values are legally notified, they can also be met. Advanced treatment systems should be considered and invested upon, if needed.

8. **Support small-and medium-scale companies in managing antibiotic discharges:** First and foremost, a nation-wide assessment should be done to understand the gaps in the capabilities of small-and medium-scale companies (particularly small manufacturing units) in treating the antibiotics they are manufacturing. Small companies manufacturing antibiotics must be supported to manage their waste well. Apart from appropriately linking their waste to nearby CETPs, they should be supported in ensuring effective primary treatment, low-cost but effective treatment approaches/technologies, appropriate segregation and process control measures. The governments may consider an incentive-based and/or financial support programme that can help them upgrade and build capacity.

Antibiotic manufacturing (API/FPP) industry in India:

9. **Invest more in process control which are preventive measures and can be cost-effective with high return on investment.** Considering no legal limits for antibiotics, process control measures are largely focussed on antibiotic recovery and reducing wastewater. This saves costs but not fully utilizes the potential of this preventive and cost-effective set of measures that can be instrumental in helping discharge become antibiotic free. Small-and medium-scale companies also appear to focus less on it. The industry big or small, should consider building in-house capacity, upgrading and investing in systems to help achieve better process control outcomes. It should also document the results for records and checks.

10. **Build in-house capacity and upgrade waste treatment systems aimed at eliminating antibiotics in manufacturing discharge.** Despite the waste management approaches claimed to have been used by industry, monitoring reveals high levels of antibiotics in manufacturing discharges, which suggests that whatever is done is inadequate to bring it under risk-free levels. Clearly, there is a need to invest in waste treatment systems and build internal capacity. This should be based on nature and scale of antibiotics produced, infrastructure/resources available and the safe levels of antibiotics in the discharge.

11. **Support surveillance, policy-making and share data.** The industry is expected to come forward and support necessary surveillance efforts related to testing as well as audits and the inspection of waste-related tests and documents. It should also facilitate policy development such as related to notification of limiting values/discharge targets and should be open to sharing all relevant data with regulatory agencies.

Annexures

Annexure 1: Global evidence on AMR-causing determinants in waste from antibiotic manufacturing, treatment plants and nearby

Country, year	Sample type, location	Key findings
China (2021)[94]	Wastewaters were collected from different treatment points of two STP and two PMFs	• STP wastewater: 19–33 types of antibiotics detected at least once; concentration upto 12.7 µ/l • PMF wastewater: 21–34 types of antibiotics detected with frequencies up to 100 per cent (conc. ranging up to 19.0 µ/l) • Fluoroquinolones and sulphonamdes dominant classes, accounting > 90 per cent of total antibiotic concentration in wastewaters
Switzerland (2020)[95]	Daily composite samples of wastewater effluent from two WWTPs (one receives discharges from pharma-ceutical production and one receives municipal waste-water)	• 10 times as many potential industrial emissions were detected as compared to the WWTP receiving purely domestic wastewater • For 11 pharmaceuticals, peak concentrations >10 µg/l and up to 214 µg/l were quantified, which are clearly above typical municipal wastewater concentrations
Croatia (2020)[96]	Sediment and wastewater samples obtained from Kalinovica creek near the city of Zagreb, where the local drug -formulation facility discharges its wastewaters; facility makes antibiotics mainly from sulfonamide, tetracycline, ß -lactam, diaminopyridine and macrolide classes. Sample collected at three sites—discharge site (DW0), upstream (UP) and 3000 m downstream of discharge (DW3000) during winter and summer	• Largest amounts of trimethoprim (up to 5.08 mg/kg) and azithromycin (up to 0.39 mg/kg) at DW0, but sulfonamides accumulated at DW3000 (total up to 1.17 mg/kg). • Quantitative PCR revealed significantly increased relative abundance of various antibiotic resistance genes (ARGs) against β-lactams, macrolides, sulfonamides, trimethoprim and tetracyclines in sediments from DW0, despite relatively high background levels of some ARGs already at UP site. • Only sulfonamide (sul2) and macrolide ARG subtypes (mphG and msrE) were still elevated at DW3000 compared to UP. • Numerous taxa with increased relative abundance at DW0 decreased to background levels at DW3000, suggesting die-off or lack of transport of effluent-originating bacteria. • In contrast, various taxa that were more abundant in sediments than in effluents increased in relative abundance at DW3000 but not at DW0, possibly due to selection imposed by high sulfonamide levels. • Network analysis revealed strong correlation between some clinically relevant ARGs (e.g. bla_{GES}, bla_{OXA}, *erm*B, *tet*39, *sul*2) and taxa with elevated abundance at DW sites, and known to harbour opportunistic pathogens, such as *Acinetobacter*, *Arcobacter*, *Aeromonas* and *Shewanella*.
Croatia (2019)[97]	Mixed liquor (i.e a mixture of wastewater and activated sludge within the aeration tank) collected from two WWTPs—one receiving wastewater from a pharma-ceutical manufacturing facility (mainly azithro-mycin) and another receiving wastewater from the city of Zagreb	• Levels of antibiotics in industrial WWTP (pharmaceutical manufacturing): o In activated sludge (ng/g): Azithromycin (4300), Erythromycin (<37) o In aqueous phase (µg/l): Azithromycin (1200), Erythromycin (4.3) • High abundance of ARGs in the WWTP receiving wastewater from macrolide production facility • Total abundance of ARGs was three times higher in sludge from WWTP receiving pharmaceutical production wastewater than in municipal sludge from the STP; total number of unique ARGs was lower in industrial compared to municipal samples • Aminoglycoside, amphenicol, sulfonamide, tetracycline and trimethoprim resistance genes were significantly more common in the industrial sludge, while the macrolide-lincosamide-streptogramin (MLS) class of genes showed significantly lower abundance in industrial compared to municipal sludge • Macrolide resistance genes did not have higher abundance in the industrial sludge, but genes associated with mobile genetic elements such as integrons did

Country, year	Sample type, location	Key findings
Vietnam (2018)[98]	Water samples collected from around the outlets of four pharmaceutical manufacturing plants	• Concentrations and detection frequency of antibiotic residues in pharmaceutical manufacturing effluent were higher than those from other sources (such as hospital and aquaculture sites) • Trimethoprim, ofloxacin, norfloxacin, ciprofloxacin present at significant concentrations in samples • Resistance to ciprofloxacin and norfloxacin by the indicator *E. coli* was only observed in samples from pharmaceutical producing sites
China (2018)[99]	Six pharmaceutical wastewater treatment plants (PWWTPs) Note: Different genes were monitored in different PWWTPs (PWWTP A: lincosamides; PWWTP B: aminoglycosides and macrolides; PWWTP C: quinolones; PWWTP D: macrolides and quinolones; PWWTP E: cephalosporins; and PWWTP F: quinolones and macrolides)	• Levels of typical ARG subtypes in the final effluents ranged from (1.03 ± 0.91) × 101 to (6.78 ± 0.21) × 107 copies/ml. Big part of the ARGs may be transported to the dewatered sludge • Bacterial abundance and antibiotic concentration within the PWWTP influenced the fate of the associated ARG together • Macrolide ARGs, positively correlate weakly with total macrolide antibiotic concentrations but positively correlate strongly with 16S rRNA concentrations • ARGs concentration in the wastewater from fermentation was significantly higher than chemical synthesis and preparation.
Pakistan (2016)[100]	Industrial wastewater from five sites in different pharmaceutical manufacturing industrial areas of Lahore	• All five sites were contaminated with oxytetracycline, doxycycline, ciprofloxacin, levofloxacin and ofloxacin • Residual levels were found in the range 0-9.40 mg/l in wastewater • Highest levels of levofloxacin (6.20 mg/l) and tetracycline (9.40 mg residues detected in the industrial wastewater
Korea (2011)[101]	Influent and effluent samples from four pharmaceutical manufacture WWTPs	• Influents: Lincosamide (0.165–671 µg/l) in six samples, ciprofloxacin • (0.528–34.6 µg/l) in five samples, florfenicol (2.28–77.5 µg/l) in five samples • Effluents: Sulfathiazole (0.028–3.96 µg/l) and florfenicol (0.033–4.61 µg/l) were detected in four samples
Taiwan (2008)[102]	Waste streams and effluents from three pharmaceutical production facilities	• 26 different antibiotics detected out of which 12 were fluoroquinolones • Concentrations of antibiotics detected (in ng/l): Sulfanilamide (50), sulfaguanidine (4), sulfadiazine (19), sulfamethxazole (22), sulfamethazine (1), tetracycline (5), clindamycin (10), erythromycin (107), clarithromycin (87), josamycin (4), cephalexin (27), cephradine (1), dimetridazole (22), nalidixic acid (7), flumequine (3), oxolinic acid (4), pipemidic acid (10), norfloxacin (9), ciprofloxacin (396), pefloxacin (12), enrofloxacin (8), ofloxacin (853), marbofloxacin (3), sarafloxacin (4), difloxacin (6), thiamphenicol (1)

Abbreviations- ARB: Antibiotic Resistant Bacteria; ARG: Antibiotic Resistant Genes; PCR: Polymerase Chain Reaction; PMFs: Pharmaceutical Manufactories; STPs: Sewage Treatment Plants; WWTP: Wastewater Treatment Plant.

Annexure 2: Studies on antibiotic residues in and around pharmaceutical manufacturing sites in India reported in literature

Study details Organization (location, year)	Sample collection type and area/site	Antibiotics detected	Levels (µg/l)
Indian Institute of Technology Hyderabad, India (Hyderabad, 2016)[103]	Outlet of Amberpet Sewage Wastewater Treatment Plant (WWTP), Hyderabad	Ciprofloxacin	5,015.6
		Enrofloxacin	181.6
		Norfloxacin	251.13
		Pefloxacin	38.33
		Difloxacin	18.91
		Lomefloxacin	10.26
		Ofloxacin	542.45
University of Gothenburg, Sweden (Telangana, 2009)[104]	Effluent from outlet of Patancheru Enviro Tech Ltd, Hyderabad	Ciprofloxacin	14,000
		Enrofloxacin	210
		Lomefloxacin	8.8
		Norfloxacin	25
		Ofloxacin	55
University of Gothenburg, Sweden (Telangana, 2007)[105]	Effluent from Patancheru Enviro Tech Ltd, Hyderabad	Ciprofloxacin	28,000-31,000
		Enrofloxacin	780-900
		Norfloxacin	390-420
		Lomefloxacin	150-300
		Enoxacin	150-300
		Ofloxacin	150-160
University of Gothenburg, Sweden (Telangana, 2011)[106]	River sediments downstream from a waste-water treatment plant (WWTP) located in Patancheru, Hyderabad	Ciprofloxacin	up to 914 µg/g organic matter
	River sediments upstream from a waste-water treatment plant (WWTP) located in Patancheru, Hyderabad	Ciprofloxacin	up to 7.1 µg/g organic matter

Annexure 3: Region-wise export of antibiotic APIs and FPPs in 2021–22

a. Export of antibiotic APIs

6 digit HS code and antibiotics	Quantity exported (MT)	Per cent of total API export*	Region-wise quantity exported (MT)								
			Asia	Africa	Latin America	North America	Europe	Australia and Oceania	European Union	G7	G20#
293590 Sulphonamides	22,687.2	69.5	3,297.5	10,295.6	4,613.2	868.9	3,592.9	19.7	3,372.5	1,381.2	3,378
294110 Penicillins and their derivatives with a penicillinic acid structure salts thereof	5,101.0	15.6	2,968.0	1,554.1	257.1	7.9	305.6	6.5	242.5	23.2	1,548.1
Total	**27,788.2**	**85.1**	**6265.5**	**1,1849.7**	**4,870.4**	**876.8**	**3,898.5**	**26.2**	**3,614.9**	**1,404.4**	**4,926.1**
Percentage of the total			**22.5**	**42.6**	**17.5**	**3.2**	**14**	**0.1**	**13**	**5.1**	**17.7**

*Total FPP export in 2021-22 was 83,291 MT; #G20 countries includes data for 18 countries; excludes India and the European Union

b. Export of antibiotic FPPs

Antibiotic formulations selected for region-wise analysis (HS code and Antibiotic)	Quantity exported (MT)	Region-wise quantity exported (MT)								
		Asia	Africa	Latin America	North America	Europe	Australia and Oceania	European Union	G7	G20#
30041030 Amoxycyllin in capsules, injections etc.	7,803.8	1,574.4	3,654.0	454.3	611.3	1,351.5	156	777.1	1,099.2	1,871.5
30041090 Other medicaments containing penicillins/ derivatives thereof with a penicillinic acid structure/ streptomycins or their derivatives put up for retail sale	8351	1,725	2,757.2	554.7	1,398.5	1,537.5	373.2	1,286.3	25,52.6	3,242.5
30042012 Cephalexin - formulations thereof, in capsules etc.	12,70.3	200.9	405.8	39.2	533.9	27.2	63.2	17.6	548.7	674.6

Antibiotic formulations selected for region-wise analysis (HS code and Antibiotic)	Quantity exported (MT)	Region-wise quantity exported (MT)								
		Asia	Africa	Latin America	North America	Europe	Australia and Oceania	European Union	G7	G20#
30042013 Ciprofloxacine- in capsule,tablets form etc.	2,578.8	725.1	1,544.1	88.6	29.4	184.9	6.7	81.3	145.2	435.1
30042019 Other cephalosporins and their derivatives	1,7017.9	5,691.2	8,445.6	432.1	654.3	1,760.6	34.1	645.2	1,007.8	25,62.8
30042020 Sulfonamides and cotrimoxazole	3,358.8	203.4	2,374.8	171.8	330.9	242.4	35.3	233.7	481.3	577.1
30042033 Ciprofloxacin (fluoroquinolones)	3,149.4	444.9	1896.3	312.3	276.5	216.8	2.5	100.5	346.7	474
30042039 Other fluoroquinolones	2210	989.6	526.2	213.8	178.8	301.2	0.1	144.2	2,21.8	414.1
30042049 Other tetracycline	1,136.6	94.8	304.9	37.4	460.5	238.7	0.3	73.4	633	6,92.3
30042064 Azithromycin	2,106.4	687.4	776.3	108.8	298.6	227.9	7.2	118.6	372.5	558.5
30049022 Metronidazole-formulations single and in combination with furazolidone and diloxanide furoate.	12,725.7	5,193.5	5,601.3	935.8	151.4	833.3	10.4	4,59.3	380.1	1,979.9
30042099 Other medicament containing other antibiotic and put up for retail sale	7,340.1	2,342.2	2,852.5	469.0	791.7	832.3	52.3	348	1,257.3	1,761.1
30049057 Other antitubercular drugs	1,727.8	579.4	832.3	122.6	0.1	164.3	29.2	141.5	2.9	210.6
30049087 Antibacterial formulations, n.e.s.	4,815.2	1,563.9	1,307.7	221.0	932.2	728.7	61.7	647.1	994.6	1,261.9
Total	**75,591.7**	**22,015.6**	**33,278.9**	**4,161.4**	**6,648.2**	**8,647.3**	**832.1**	**5,073.8**	**10,043.7**	**16,716**
Percentage of the total		**29.1**	**44.0**	**5.5**	**8.8**	**11.4**	**1.1**	**6.7**	**13.3**	**22.1**

*Total FPP export in 2021-22 was 83,291 MT; #G20 countries includes data for 18 countries; excludes India and the European Union

Annexure 4. Antibiotic APIs imported and exported in 2021–22

Antibiotic class (Quantity of API imported/exported in MT, per cent of total antibiotic import/export*)	Antibiotic APIs imported (per cent of respective class)	Antibiotic APIs exported (per cent of respective class)
Penicillins Import: 14700.66, 46.25 per cent Export: 5101, 15.64 per cent	6 – aminopenicillinic acid (APA) (45.98 per cent), Penicillins and its salts (44.64 per cent), Other penicillins and their derivatives with a penicillinic acid structure salts thereof (4.87 per cent), Amoxycillin and its salts (4.35 per cent), Ampicilline and its salts (0.13 per cent), Cloxacilline and its salts (0.03 per cent)	Amoxycillin and its salts (55.31 per cent), Other penicillins and their derivatives with a penicillinic acid structure salts thereof (24.11 per cent), Ampicillin and its salts (10.36 per cent), Cloxacillin and its salts (10.20 per cent), Penicillins and its salts (0.02 per cent)
Other antibiotics Import: 9809.93, 30.86 per cent Export: 2820.59, 8.65 per cent	N.S.	N.S.
Sulphonamides Import: 2118.01, 6.66 per cent Export: 22687.11, 69.55 per cent	Other (78.05 per cent), Sulphadimidine (10.92 per cent), Sulphamide (6.68 per cent), Sulphadiazine (3.49 per cent), Sulphamethoxazole (0.86 per cent)	Other (82.42 per cent), Sulphamethoxazole (17.30 per cent), Sulphadiazine (0.26 per cent), Sulphadimidine (0.02 per cent)
Macrolides and ketolides Import: 1756.29, 5.53 per cent Export: 648.9, 1.99 per cent	Erthyromycin and its derivatives salts thereof (100 per cent)	Erthyromycin and its derivatives salts thereof (100 per cent)
Tetracyclines Import: 1295.36, 4.08 per cent Export: 33.91, 0.10 per cent	Tetracycline/oxytetracycline and their salts (45.66 per cent), Doxycylime and its salts (29.43 per cent), Other tetracyclines and their derivatives salts (24.90 per cent)	Tetracycline/oxytetracycline and their salts (69.92 per cent), Doxycyline and its salts (29.46 per cent), Other tetracyclines and their derivatives salts (0.62 per cent)
Ansamycins Import: 840.52, 2.64 per cent Export: 113.75, 0.35 per cent	Other rifampicin and its salts (64.34 per cent), Rifampicin (31.44 per cent), Rifa or rifa s sodium (rifaint) (4.22 per cent)	Other rifampicin and its salts (50.09 per cent), Rifampicin (49.66 per cent), Rifa or rifa s sodium (rifaint) (0.25 per cent)
Aminoglycosides Import: 572.77, 1.80 per cent Export: 4.59, 0.01 per cent	Streptomycins (48.15 per cent), Neomycin (33.16 per cent), Gentamycin and its salts (15.06 per cent), Other streptomycine and drvtvs, salts (3.63 per cent)	Neomycin (41.83 per cent), Other Streptomycin and derivatives, salts (36.82 per cent), Gentamycin and its salts (18.30 per cent), Streptomycins (3.05 per cent)
Fluoroquinolones Import: 310.93, 0.98 per cent Export: 1024.19, 3.14 per cent	Ciprofloxacin and its salts (73.03 per cent), Norfloxacin and its salts (26.97 per cent)	Ciprofloxacin and its salts (94.63 per cent), Norfloxacin and its salts (5.36 per cent)
Cephalosporins Import: 288.22, 0.91 per cent Export: 147.81, 0.45 per cent	Cephalexin and its salts (100 per cent)	Cephalexin and its salts (100 per cent)
Amphenicols Import: 94.27, 0.30 per cent Export: 37.53, 0.12 per cent	Chloramphenicol and its derivatives salts thereof (100 per cent)	Chloramphenicol and its derivatives salts thereof (100 per cent)

Source: Export Import data bank (Annual), Department of Commerce, Govt. of India; N.S.: Not Specified

*Total antibiotic API import in 2021–22 is 31,786.96 MT; Total antibiotic API export in 2021–22 is 32,619 MT

Annexure 5. Antibiotic FPPs imported and exported in 2021–22

Antibiotic class (Quantity of FPPs imported/exported in MT, per cent of total antibiotic import/export*)	Antibiotic FPPs imported (per cent of respective class)	Antibiotics FPPs exported (per cent of respective class)
Cephalosporins Import: 289.56, 37.12 per cent Export: 18499.34, 22.21 per cent	Other cephalosporins and their derivatives (100 per cent)	Other cephalosporins and their derivatives (91.99 per cent), Cephalexin - formulations thereof, in capsules etc. (6.87 per cent), Cefadroxil (0.90 per cent), Cefazolin (0.20 per cent), Cefoxitin (0.04 per cent)
Antibacterial formulations n.e.s Import: 238.57, 30.58 per cent Export: 4815.2, 5.78 per cent	N.S.	N.S
Others Import: 123.77, 15.87 per cent Export: 7553.98, 9.07 per cent	Other medicament containing other antibiotic and put up for retail sale (94.63 per cent), Other, containing antibiotics (29.14 per cent)	Other medicament containing other antibiotic and put up for retail sale (97.17 per cent), Other, containing antibiotics (2.13 per cent)
Lincosamides Import: 70.55, 9.04 per cent Export: 305.51, 0.37 per cent	Clindamycin (100 per cent)	Clindamycin (100 per cent)
Penicillins Import: 32.13, 4.12 per cent Export: 18940.83, 22.74 per cent	Penicillin in capsules, injections etc. (36.91 per cent), moxycyllin in capsules, injections etc. (34.80 per cent), Other medicaments containing penicillins/derivatives thereof with a penicillinic acid structure/streptomycins or their derivatives put up for retail sale (28.10 per cent), Medicaments containing penicillins/their derivatives with a penicillinic acis structure, streptomycns/their derivatives (0.16 per cent), Cloxacillin in capsules, injections etc. (0.03 per cent), Ampicillin in capsules, injections etc. (0)	Other medicaments containing penicillins/ derivatives thereof with a penicillinic acid structure/streptomycins or their derivatives put up for retail sale (44.09 per cent), Amoxycyllin in capsules, injections etc. (41.20 per cent), Amclos in capsules injections etc. (4.09 per cent), Ampicilline in capsules, injections etc. (3.78 per cent)c, Penicillin in capsules, injections etc. (3.10 per cent), Cloxacillin in capsules, injections etc. (2.81 per cent), Medicaments containing penicillins/their derivatives with a penicillinic acid structure, streptomycins/their derivatives (0.92 per cent), Becampicillin (0.01 per cent)
Macrolides and ketolides Import: 9.89, 1.27 per cent Export: 3196.91, 3.84 per cent	Azithromycin (94.94 per cent), Clarithromycin (4.95 per cent), Erythromycin in capsules, injections, ointments etc. (0.10 per cent)	Azithromycin (65.89 per cent), Erythromycin in capsules, injections, ointments etc. (22.00 per cent), Clarithromycin (7.22 per cent), Other macrolide (4.45 per cent), Roxithromycin (0.44 per cent)
Nitroimidazoles Import: 9.68, 1.24 per cent Export: 13059.49, 15.68 per cent	Metronidazole-formulations single and in combination with furazolidone and diloxanide furoate (99.03 per cent), Secnidazole (1.07 per cent)	Metronidazole-formulations single and in combination with furazolidone and diloxanide furoate (97.44 per cent), Tinidazole - formulations including combination formulations with diloxa nide furoate/ furazolidone/antibacter (2.07 per cent), Secnidazole (0.49 per cent)
Fluoroquinolones Import: 2.48, 0.32 per cent Export: 8544.35, 10.26 per cent	Other fluoroquinolones (93.55 per cent), Ciprofloxacin in capsules, tablets form etc. (5.65 per cent), Ciprofloxacin (fluoroquinolones)(0.81 per cent)	Ciprofloxacin (fluoroquinolones) (36.86 per cent), Ciprofloxacin- in capsules, tablets form etc. (30.18 per cent), Other fluoroquinolones (25.86 per cent), Ofloxacin (4.60 per cent), Norfloxacin (2.02 per cent), Nalidixic acid (0.47 per cent)
Other antiTB drugs Import: 1.79, 0.23 per cent Export: 1727.75, 2.07 per cent	N.S.	N. S

Antibiotic class (Quantity of FPPs imported/exported in MT, per cent of total antibiotic import/export*)	Antibiotic FPPs imported (per cent of respective class)	Antibiotics FPPs exported (per cent of respective class)
Tetracyclines Import: 1.04, 0.13 per cent Export: 1339.77, 1.61 per cent	Other tetracycline (100 per cent)	Other tetracycline (84.83 per cent), Oxytetracycline (13.42 per cent), Chlortetracycline (1.74 per cent)
Glycopeptides Import: 0.430, .06 per cent Export: 644.26, 0.77 per cent	Vancomycin (100 per cent)	Vancomycin (100 per cent)
Sulphonamides Import: 0.20, 0.03 per cent Export: 3358.8, 4,03 per cent	Sulfonamides and cotrimoxazole (100 per cent)	Sulfonamides and cotrimoxazole (100 per cent)
Drugs used to treat TB Export: 2182.96, 2.62 per cent		Isoniazid (61.90 per cent), Pyrazinamide and ethambutol (14.38 per cent), Isoniazid (14.32 per cent), Ethambutol (5.51 per cent), Pyrazinamide (3.90 per cent)
Amphenicols Export: 432.53, 0.52 per cent		Chloramphenicol capsules, injections etc. (100 per cent)
Sulfa drugs n.e.s. Export: 228.05, 0.27 per cent		N.S.
Polymyxins Export: 86.98, 0.19 per cent		Polymyxin B and Colistin (100 per cent)
Ansamycins Export: 72.74, 009 per cent		Rifampicin (95.01 per cent), Rifampicin (4.99 per cent)
Aminoglycosides Export: 29.46, 0.04 per cent		Streptomycins and its salts in capsules, injections, etc. (99.53 per cent), Streptomycin (0.48 per cent)

Source: Export Import data Bank (Annual), Department of Commerce, Govt. of India; N.S.: not specified
*Total antibiotic FPPs import in 2021-2022 is 780.9 MT; Total antibiotic FPPs export in 2021-2022 is 83291 MT

Annexure 6: List of companies which manufacture or market select antibiotics in India

Azithromycin (21)	Ofloxacin (27)	Ciprofloxacin (21)	Ceftriaxone (16)	Isoniazid (20)	Co-trimoxazole (9)	Amoxicillin (27)	Ampicillin (19)
Aceso Pharma Pvt Ltd	Apple Therapeutics Pvt Ltd	Abbott Healthcare Generics	AKS Life Global Pvt Ltd	Acme Pharmaceuticals	Agnus Pharmaceuticals	ABL Lifecare Pvt Ltd	Alembic Generics
Advok Pharmacia Pvt Ltd	Aristo Pharmaceuticals	Alembic Generic	Belvedere Healthcare Pvt Ltd	Alves Healthcare	Alembic Generic	Allure Remedies Pvt Ltd	Aristo Pharmaceuticals Ltd
Anista Healthcare	Aspire Remedies Pvt Ltd	Arbro Pharmaceuticals Ltd	Bestochem Formulation (I) Ltd	Aristo Pharmaceuticals Ltd	Artura Pharmaceuticals	Biochem (Generics)	Biocare Remedies
Belvedere Healthcare Pvt Ltd	Biogensis Biotechnic	Bestochem Formulation Ltd	Cadila Generic	Cadila (Zydus)	Hindustan Antibiotics	Depri Pharmaceuticals	Biochem Pharmaceuticals Ind
Cipla Ltd	Caddix Healthcare	Biochem (Generics)	Daksh Pharmaceuticals Pvt Ltd	Cipla Ltd	Omega Biotech Ltd	Galpha Laboratories Pvt Ltd	Cadila Pharma
Conch Healthcare	Cipla Ltd	Cadila Pharma	Elis Pharma India Pvt Ltd	Globus Healthcare	Ridley Lifesciences Pvt Ltd	Generic Dealer	Cipla Generics
Gentech Healthcare Pvt Ltd	Conch Healthcare	Leben Laboratories Pvt Ltd	Elwin (Zee Lab)	Kentreck Laboratories Pvt Ltd	Synokem Pharmaceuticals Pvt Ltd	Genetech Biotech Pvt Ltd	Cubit Healthcare
Genuine Bio Life Sciences Pvt Ltd	Curewell Drugs & Pharmaceuticals	Magma Allianz Laboratories Limited	Gentech Healthcare Pvt Ltd	Lancer Therapeutics	Vensat Pharma (Madhav Biotech)	Hi Cure Biotech	HICURE Pharmaceuticals Pvt Ltd
Higlance Laboritories Ltd	Garglance Biotech	Med Manor Organics (Med Star)	Gladcare Formulation Pvt Ltd	Lupin Pharma	Virchow Healthcare Pvt Ltd	Indoco Remedies Ltd	Hindustan Antibiotics
Ikon Remedies Pvt Ltd	Intas Generic	Medispan Ltd	Glantis Pharmaceutical	Macleods Pharmaceuticals Ltd		Insinus Pharmaceuticals	IPCA Labs Ltd
JES pharmacia Pvt Ltd	Leeford Healthcare Ltd	Midas Healthcare	Healthkind Labs Pvt Ltd	Medispan Limited		Intas Pharma (Generics)	Kentreck Laboratories Pvt Ltd
Mavin Pharmaceutical	Macleods Pharma	Optho Remedies	Maxcare Labs	Merind Wockhardt Ltd		Leeford Healthcare Ltd	Octavia Labs Pvt Ltd
Medley (Generics)	Mankind Pharmaceuticals Pvt Ltd	Punjab Formulations Ltd	Organic Labs Pvt Ltd	Overseas Healthcare Pvt Ltd		Lifegrace Pharmaceuticals Pvt Ltd	Panjon Biocare
Paramount Healthcare	Medley Pharmaceuticals Pvt Ltd	Sapinox (Division of Magma alliance)	Searle Interphar (Scott-EDIL)	Pfizer Limited		Macro Pharmaceuticals	Scala Pharma
RTN pharma	Morepen Lab Generic	Searle Interphar	Univentis Medicare Limited	Sandoz Pvt Ltd		Medpure Healthcare	Searle Interphar (SCOTT-EDIL)
Sapinox (Division of Magma Allianz)	Opticarma (India) SMC Pvt Ltd	Simpex Pharma	V- Revive Medicure Pvt Ltd	Shreya LifeSciences Pvt Ltd		Merelin Pharma	Sun Pharma
Sofi Healthcare LLP	Osrik Bio Lifesciences	Sun Pharma		Sun Pharma		Moon Mark Remedies	Symet Drugs Ltd
SOTAC pharma	Rosette Aeon Lifecare	Torque Pharmaceuticals Pvt Ltd		Sunij Pharma		Morepen Lab Generic	VEE Excel Drugs and Pharmaceuticals Pvt Ltd
Trugen Neuroscience Pvt Ltd	Sac Pharmaceuticals	TOSC international		Svizera Healthcare		Red Plus Pharma	Walter Bushnell Ltd
V-Revive Medicure Pvt Ltd	Senses Pharmaceuticals Ltd	Unichem Generics		Vee Excel Drugs and Pharmaceuticals Pvt Ltd		Resolute Healthcare	
Yours Medicare Pvt Ltd	Sky Lab Lifesciences	Wings Pharmaceuticals Pvt Ltd				Rosette Aeon Lifecare	
	Srigan Anatto care Pvt Ltd					Searle Interphar	
	Sun Pharma (Milmet)					Synergenix India	
	Torque Pharmaceuticals Pvt Ltd					Trans Lifesciences	
	Trugen Neurosciences Pvt Ltd					Vista LifeSciences Pvt Ltd	
	Zydica Healthcare					Yours Medicare Pvt Ltd	
	Zydus Cadila					Zydica Healthcare	

Cefotaxime (19)	Metronidazole (25)	Clindamycin (26)	Chloramphenicol (24)	Rifampicin (25)	Erythromycin (24)	Levofloxacin (27)	Colistin (24)
Ajanta Pharma Ltd	Angus Pharmaceuticals	Addsum LifeSciences Pvt Ltd	Abbott Laboratories Ltd	Acme Pharmaceuticals	Abdiel (India)	Aristo Pharmaceuticals Ltd	Afive Pharmaceuticals
Ampra Pharmaceuticals Pvt Ltd	Baxter (India) Ltd	Aero Chem	Agarwal Drugs Pvt Ltd	Angus Pharmaceuticals	Acinom Healthcare	Aspire Remedies Pvt Ltd	Alde Medi Impex Ltd
Aventis Pharma (Hoechst)	Bionova Lifesciences	Aveta Pharma Pvt Ltd	Alkem	Aristo Pharmaceuticals Ltd	Aden Healthcare	Atra Pharmaceuticals	American Biocare
Elder Pharmaceuticals	Cadila Pharma	Bionova LifeSciences	Alkem Laboratories Ltd	Briskon Laboratories	Galderma india Pvt Ltd	Biochem (Generics)	Bestochem Formulation Ltd
Indkus Biotech India	Cipla Generic	Carlton Dermatology	Archicare Ltd	Cadila (Zydus)	Glaxo Smithkline (GSK)	Cadman Healthcare	BMW Pharmaco India Pvt Ltd
IPCA Labs	Daksh Pharmaceuticals Pvt Ltd	Cucard	Aronex LifeSciences Pvt Ltd	Cadila Pharma	Hamax Pharmaceuticals	Chemo Drugs	Esquire Drug House
Jeen Healthcare	Dream India Pharmecuticals	Daksh Pharmaceuticals Pvt Ltd	Arvincare Healthcare	Cipla Ltd	Imported Medicine Dealer	Dream India Pharmaceuticals	Excel Waves labs pvt ltd
Lupin Maxter Ltd	Eskag Pharma Pvt Ltd	DCGI Formulations	Bestochem Formulations Ltd	Emil Pharma	Indamed Pharmecuticals pvt Ltd	Eden Healthcare	Fornex Healthcare Pvt Ltd
Mano (Orchid)	Glaxo SK 4	Foregen Healthcare	Biosearch Organics Ltd	Globus Healthcare	Indica Laboratories Pvt Ltd	Edmund Healthcare Pvt Ltd	Grampus Laboratories
Nac International Ltd	Kentreck Laboratories Pvt Ltd	Galpha Laboratories Pvt Ltd	Chem Biotech Healthcare	Indoco remedies Ltd	Indoco Remedies Ltd	Five flags Healthcare	Indu Drugs
Neon Laboratories Pvt Ltd	Kivi Labs	Gujarat Pharma Labs Pvt Ltd	Davis Morgan Labs	Kopran Laboratories Ltd	IPCA labs ltd	Ikon Remedies Pvt Ltd	Innovative Pharmaceuticals
Nicholas Piramal India Ltd	Lancer Therapeutics	HBC Dermiza Healthcare	Densa Pharmaceuticals Pvt Ltd	Lancer Therapeutics	Jenburkt Pharmaceuticals	J.B Lifesciences	La Renon Healthcare Pvt Ltd
Pharma Impex Laboratories Ltd	Lark Laboratories (India) Ltd	Ikon Remedies Pvt Ltd	Dolvis Bio Pharma Pvt Ltd	LifeLine Biotech Ltd	Kems Pharma	Kentreck Laboratories Pvt Ltd	Mankind Pharmaceuticals Ltd
Reco drugs (Div of Sachon Pharma)	Lumax pharmaceut-icals	Iskon LifeSciences	Eastern Capsulations Pvt Ltd	Lupin Pharma	Kopran Laboratories Ltd	Leeford Healthcare	Mediyork Pharma Pvt Ltd
Scott-EDIL	Mankind Lifestar	Kurit Pharma	Events Pharmaceuticals Pvt Ltd	Medispan Ltd	Mednext Pharma Pvt Ltd	Morepen Labs Ltd	Neovet
Pharmacia Ltd	Morepen Lab	Leeford Healthcare Ltd	Galpha Laboratories Pvt Ltd	Merind	Mercury Healthcare Pvt Ltd	Oshine Pharmaceuticals Pvt Ltd	Nutal Lifesciences
Silicon Pharma	Generic	Lupin Maxter Ltd	Glow vision pharma-ceutical	Wockhardt Ltd	Minopharm Laboratories Limited	Pharmanova India Drugs pvt ltd	Pride Healthcare
Solitare Pharma	Nestor Pharmaceuticals Ltd	Mavin Pharmaceutical	Nukind Healthcare	Overseas Healthcare Pvt Ltd	Psyco remedies	Razcon (Magma allainz lab ltd)	Rekin Pharma Pvt Ltd
Tablets (India) Ltd	Paam Pharmecuticals Ltd	MITS Healthcare Pvt Ltd	Rynel Clifton Pharma	Sandoz Pvt Ltd	Renaigate Pharmikia	Remedium Healthcare Pvt Ltd	Rivpra Formulation
Zee Laboratories	Que Pharma Pvt Ltd	Pfedex	Search Orbis Pharmaceuticals	Shreya Lifescience Pvt Ltd	Searle Interphar	Rhydburg Pharmaceuticals Ltd	Samarth lifesciences Pvt Ltd
	Rhydburg Pharmecuticals Ltd	Skin Venture	Senses Pharmaceutical Ltd	Sun Pharma	Sun Pharmaceuticals India Ltd	RoseLabs Healthcare Pvt Ltd	Signity Pharmaceuticals Pvt Ltd
	Searle Interphar (Scott-EDIL)	Systopic Laboratories Pvt Ltd	Sun Pharma	Sunij Pharma	Svizera Healthcare	Rudolf Lifesciences Pvt Ltd	Simpson and Brawn Pharmaceuticals
	Torque Pharmaceuticals Pvt Ltd	Torque Pharmaceuticals Pvt Ltd	Ultramax Healthcare Pvt Ltd	Svizera Healthcare	Systopic Laboratories Pvt Ltd	Talent Healthcare Ltd	Solitare Pharmacia Pvt Ltd
	Univentis medicare Limited	USV Ltd	Vesta Biotech Pvt Ltd	Vee Excel Drugs and Pharmaceuticals Pvt Ltd	USV Ltd	Ultimate Heathcare	Stanford Laboratories Pvt Ltd
	Vintage Labs Pvt Ltd	Vesta Biotech Pvt Ltd				Uniqlife Biosciences Pvt Ltd	Uko Pharmaceuticals Pvt Ltd
	Zenia Pharmaceuticals	Vistica LifeSciences				V-Revive Medicure Pvt Ltd	Wallace Pharmaceuticals Ltd
						Zing lifecare Pvt Ltd	Wens Drugs (India) pvt Ltd
							Zyphar's Pharmaceuticals Pvt Ltd

Piperacillin (27)	Nitrofurantoin (25)	Cefuroxime (27)	Cefixime (22)	Meropenem (21)	Vancomycin (23)	Gentamycin (25)	Amikacin (25)
Addil Biotech Pvt Ltd	Alexia Pharma	Aden Healthcare	Abbott	Allenchem	Adley formulation	Amrut Drug	Abbott
AMN Lifesciences	Apcon Remedies	Apex Organics	Algen Remedies	Pharma	Apikos Pharma	Research Lab Pvt	Laboratories Ltd
Antila LifeSciences	Arbutus Healthcare	Apoorv Nutra Pharm	Pvt Ltd	Avni Healthcare	Bharat Antibiotics	Ltd	Abiba Pharmacia
Pvt Ltd	Pvt Ltd	Pvt Ltd	Austro Labs	Dream India	Biochem	Avni Pharma	Pvt Ltd
Bio Organic	CMG Biotech Pvt Ltd	Biochem (Generics)	Bestochem	Pharmaceuticals	Pharmaceuticals	Biophar	Alembic Chemical
Lifesciences	Glaxo SmithKline	Bluebug Lifesciences	Formulation Ltd	Dycine	Ind	Lifesciences	Works
Bio Zenesis Healthacre	(GSK)	Pvt Ltd	Biogensis	Pharmaceuticals	BMW Pharmaco	Cadex Laboratories	Atlantis
Biocare Remedies	Grandsure Pharma	Entod	Biotechnic	Limited	India pvt Ltd	CFL	Pharmacorp Inc
Biophar Lifesciences	Grefith LifeSciences	Pharmaceuticals Ltd	Conch	Elis Pharma india	Chandra Bhagat	Pharmaceuticals	Beatus Healthcare
BMW Pharmaco India	Pvt Ltd	Healthkind Labs Pvt	Healthcare	pvt Ltd	pharma pvt Ltd	Ltd	Pvt Ltd
Pvt Ltd	Imported Medicine	Ltd	Crestmed	Events	Eli Lilly and Comp	Fantabulous	Biotrendz
Dream India	Dealer	Human Bio Organics	Pharmaceuticals	Pharmaceuticals	Pvt Ltd	Pharma	Medicaments
Pharmaceuticals	IND- Swift Ltd	Pvt Ltd	FDC ltd	Pvt Ltd	Emcure	Gujarat Pharma	Briskon
Edward Young Labs	Johnson & Johnson	Iscon Lifesciences	Genuine Bio	Gentech Biotech	Pharmaceuticals	Lab Pvt Ltd	Laboratories
Fair Ford	(Ethnor)	J.B Lifesciences	LifeSciences Pvt	Pvt Ltd	Excel La	H&H	Cadila Pharma
Pharmaceuticals	Leogenic Healthcare	JM Pharma	Ltd	Healthkind Labs	Lifesciences	Pharmaceuticals	Concept Generic
Gentech Healthcare	Lifecred Healthcare	Kaplin Healthcare	Medley	Pvt Ltd	Fantabulous	Pvt Ltd	Curemax (Solitare
Pvt Ltd	Pvt Ltd	Pvt Ltd	(Generics)	Hitashi	Pharma	Kaiser Drugs Pvt	Pharma)
Herbert Biotech	Mediarch Healthcare	Laxon Drugs Pvt Ltd	Mint	Pharmaceuticals	Flagship Biotech	Ltd	Earum Pharma
Indkus Biotech India	Pvt Ltd	Macleods	LifeSciences Pvt	Human Bio	Galice Labs	Laborate Pharma	Elwin (Zee Lab)
Lia LifeSciences Pvt	Medrhans	Pharmecuticals Ltd	Ltd	Organics Pvt Ltd	H&Care Incorp	Magnet Labs	Elysium Pharma
Ltd	Pharmceuticals Pvt	Maneesh Healthacre	Narankaa	Maxcare Labs	Kenn pharmaceut-	Martin Brown Bio	Flora Biotech
Login Pharma Pvt Ltd	Ltd	Mavin	Pharma	Pharmakon	ical	Sciences	Gentech Biotech
Magma Allianz	Pacitora Biotech	Pharmaceutical	Novagen Pharma	Lifesciences	Marc Laboratories	MDPL	Pvt Ltd
Laboratories Limited	Sarvit LifeSciences	Omenta Pharma	ORN Remedies	Rencord	Mednext Pharma	Medico Healthcare	Gentron
Maxcare Labs	Pvt Ltd	Oster Remedies	Pvt Ltd	LifeSciences	Pvt Ltd	Mefro Dermacare	Pharmaceuticals
Mefro Pharma	Sun Pharma	Raymedica	Osrik	RKG Pharma Pvt	Mylan	MITS Healthcare	Higlance
Nucleus Inc	Syndicate	Pharmaceuticals	BioLifeSciences	Ltd	Pharmaceuticals	Pvt Ltd	Laboratories Pvt
Pharmakon	LifeSciences	Research Medicine	Oster Remedies	Ronyd Healthcare	Pvt Ltd	Nem lab	Ltd
Lifesciences	Troikaa Parenterals	Pvt Ltd	Ranbaxy	Pvt Ltd	Panacea Biotech	Parry	IG Remedies
Regalia	VHL Pharmaceuticals	Resolute Healthcare	Generics	Septalyst	Ltd	Nutraceuticals	Lupin Ltd
Pharmaceuticals Pvt	Walter Bushnell Ltd	Rosette Aeon	Sofi Healthcare	LifeSciences Pvt	Research Medicine	Perch Labs	Medispan Ltd
Ltd	XEMS (division of	Lifecare	LLP	Ltd	Pvt Ltd	Psychotropics	Pharmakon
Rouzel Pharma	Corona Remedies)	Sanify Healthcare	Sterkem Pharm	Wonder Asrox	Rosswelt	India	Lifesciences
RSM Enterprises	Ytiliga Pvt Ltd	Pvt Ltd	Pvt Ltd	Healthcare	Biosciences	Scoria	Reze Pharma
Synonn Lifesciences	Zeuson Medicines	Sapinox (Division of	Sun Pharma	Zanetaz Medicorp	Strathspey Labs	Pharmaceuticals	RSM Enterprises
Limited	Pvt Ltd	Magma Allianz)	Trugen	Zing Lifecare Pvt	Pvt Ltd	Pvt	Sarmain Pharma
Truworth Healthcare	Zydus (Corza)	Symbiosis	Neuroscience	Ltd	VHB lifesciences	Searle Interphar	Wockhardt
Wonder Asrox		Healthcare	Pvt Ltd	Zymes	Inc	Sun Pharma	Generic
Healthcare		Tansy Molequle	Zycus	BioSciences Pvt	Voopar Lifesciences	Torque	Wonder Esrox
		Wewell Biotech Pvt	LifeHealthcare	Ltd	Pvt Ltd	Pharmaceuticals	Healthcare
		Ltd	Pvt Ltd		Wyeth Lederle Ltd	Pvt Ltd	
						Will Impex	

Source: Medicea app; Note: List is non-exhaustive; based on information available from the app

Annexure 7: Costing details for Jeedimetla Effluent Treatment Limited

Costing for low TDS, COD effluent (per 10,000 litres)		**Costing for high TDS, COD effluent (per 9500 to 10,000 litres)**	
COD (ppm)		**COD (mg/l)**	
1 to 5,000 5,001 to 10,000 10,001 to 15,000	Rs 900 Rs 1,020 Rs 1,150	For COD levels > 10,001 10,001 to 50,000 50,001 to 1,00,000 1,00,001 to 1,50,000 >1,50,000	Rs 15,000 Rs 90 per tanker per 1,000 units of COD or part thereof (over 10,000 ppm of COD) Rs 3,600 + Rs 130 per tanker per 1000 units of COD or part thereof (over 50,000 ppm of COD) Rs 10,100 + Rs 400 per tanker per 1000 units of COD or part thereof (over 100000 ppm of COD) Rs 30,100 + Rs 800 per tanker per 1,000 units of COD or part thereof (over 1,50,000 ppm of COD)
TDS (ppm)		**TDS (specific gravity)** (This is as per the specific gravity the salts that are generated as a result of evaporation of the high TDS effluent)	
Upto 2,100 2,101 to 5,000	Nil Rs 300	1.05 1.10 1.20	Rs 2,400 Rs 4,800 Rs 9,600
		pH	
		5.5 to 9.0 9.01 to 10.00 <5.5 and 10.01 and above	No charge Rs 1,000 Rejected
Treatment Surcharge	Rs 800	**Treatment Surcharge**	Rs 800

Note:

1. High TDS effluent having more than 50,000 mg/l of COD will be accepted at the sole discretion of the treatment company.

2. These rates are not taking into consideration penalty charges, cost for rejection tankers.

For example, for effluent with COD value of 6,000 ppm and TDS 3,000 ppm, the cost per tanker (capacity of 10 KL) would be Rs 2,120 (1020+300+800), which would effectively be Rs 20 paisa per litre.

Similarly for effluent with COD value of 20,000 mg/l, TDS with which salts are generated for 1.05 specific gravity and the pH 7, the cost per tanker would be approximately Rs 19,000 (15,000+900+2,400+800) which would effectively be Rs 2 per litre.

Annexure 8: Assessment of select advanced wastewater treatment technologies[107,108]

Technology	Principle/mechanism	Advantages/disadvantages
Advanced Biological Processes		
Membrane bioreactor (MBR)	A process that combines microfiltration or ultrafiltration membrane unit with a suspended growth bioreactor	**Advantages** • Low-footprint, compact, high effluent quality, high volumetric load possible, high rate of degradation • Low sludge production • >90 per cent removal efficiencies for TSS and total COD when coupled with conventional activated sludge reactor **Disadvantages** • Aeration limitations • Stress on sludge in external MBR • Membrane pollution • High energy consumption, high installation and maintenance costs
Membrane technology		
Membrane technology (Microfiltration (MF), Ultrafiltration (UF), Nanofiltration (NF) and Reverse Osmosis (RO))	Separation with semi-permeable barrier	**Advantages** • Simple, fast and efficient process with no requirement of chemicals • MF/UF can be used in case of space limitations and/or variable feed water quality • NF/UF can be used in wastewater reclamation and drinking water purification **Disadvantages** • High requirement of energy; limited flow rates • High cost of investment, maintenance and operation • Fouling effect possible • High flow rate can damage shear sensitive material
Activated Carbon Adsorption		
Activated carbon adsorption	This involves an adsorption process by which molecules, atoms, or ions are adsorbed or adhere to the surface of the activated carbon particles; it makes use of powdered activated carbon or granular activated carbon	**Advantages** • Highly effective process; faster kinetics • Good ability to separate wide range of contaminants (heavy metal, organic pollutant) • Simple equipment • Good quality of treated effluent **Disadvantages** • Larger waste volumes can require vast amounts of carbon filters • Expensive to operate and maintain owing to frequent replacement or regeneration of the carbon media • Processing of adsorbent is required after wastewater treatment, for example, for incineration or regeneration. • Carbon filtration also creates filter waste that needs to be shipped off-site for disposal/incineration or regenerated on-site, resulting in another API-contaminated waste stream requiring management and disposal • May not be adequate to reduce all types of APIs to safe levels • Difficulty in absorbing compounds with low molecular weight and high solubility

Technology	Principle/mechanism	Advantages/disadvantages
Advanced Oxidation Processes		
Fenton's oxidation treatment	This involves the reaction of hydrogen peroxide with ferrous (Fe^{2+}) or ferric ions (Fe^{3+}) via a free radical chain reaction which produces hydroxyl radicals. It is a heterogeneous catalytic reaction in which iron acts as a catalyst.	**Advantages** • Reactive radicals such as hydroxyl radicals are produced in in-situ • No sludge production and mineralization of organic contaminants • Rapid degradation for recalcitrant compounds **Disadvantages** • Unknown by-products formed that need further analysis and study • High pH dependency • Ferrous sludge generated due to presence of iron • High concentration of anions formed in the treated wastewater
Heterogeneous photocatalysis	Photo-catalysis involves the acceleration of a photochemical transformation by the action of catalyst such as TiO_2 (semiconducting material) or Fenton's reagent. If the photocatalyst and the reaction medium are not in the same phase, then it is called as heterogeneous photocatalysis.	**Advantages** • Photocatalyst (e.g., TiO_2, ZnO) shows good stability in the aqueous phase • It has high activity and is non-toxic in nature • Photocatalysist is recoverable and recyclable • It is low cost and easy to operate; process highly energy efficient **Disadvantages** • High concentrated organic pollutants is poorly treated • Lack of studies on the chemical structure and toxicity of the degraded by-product • Resources such as sunlight, oxygen and photocatalyst are required in abundance
Ozonation	Involves the process of oxidation using ozone, a very strong oxidizing agent that either decomposes in water to form hydroxyl radicals that are stronger than ozone itself, thus inducing the so called indirect oxidation, or attacks, selectively, certain functional groups of organic molecules through an electrophilic mechanism	**Advantages** • Very short time to break down antibiotics **Disadvantages** • Degraded by-products can accumulate in water which needs further treatment • Most of the time, oxidation only applies to break down microorganisms. Cannot be employed in all circumstances (amides are ozone resistant) • It presents limitations in the treatment of organic compounds in highly concentrated wastewater[109]
Electrochemical oxidation	This is an oxidation process based on electrochemical method. It includes anode and cathode, connected to a power source. When an energy input and sufficient supporting electrolyte are provided to the system, strong oxidizing species are formed, which interact with the contaminants and degrade them. Hydroxyl radical is produced in situ as main oxidant. Refractory compounds are converted into reaction intermediates and, ultimately, into water and CO_2 by complete mineralization	**Advantages** • No sludge produced • Has shown complete degradation in case of certain antibiotics present in simulated waste **Disadvantages** • More expensive than Fenton's oxidation • Electrodes need to be carefully selected for process to be efficient

Technology	Principle/mechanism	Advantages/disadvantages
Wet air oxidation	This is a thermochemical process where hydroxyl radicals and other active oxygen species are formed at elevated temperatures (200–320 °C) and pressures (2–20 MPa).	**Advantages** • Insoluble organic material is able to be converted to simpler soluble compounds without hazardous substances emission • Suitable for effluent that is too toxic for biological treatment and also for effluent that is too low in concentration for incineration • Applicability to remove COD to a great extent. **Disadvantages** • High pressure and energy-intensive conditions • pH dependence • Unable to achieve full mineralization

Annexure 9: Antibiotic degradation in pharmaceutical wastewater with advanced wastewater treatment technologies

Technology	Sample type (Country, Year of study)	Antibiotic(s)	Removal efficiency
High frequency ultrasound	Simulated pharmaceutical wastewater (Colombia, 2016)	Oxacillin[110]	99.9 per cent
Sono-photocatalysis and solar sono-photocatalysis	Real industrial wastewater of amoxicillin producing batch collected from pharmaceutical industry area (India, 2020)	Amoxicillin[111]	50 per cent degradation in 10 min; >80 per cent degradation in 30 min; 95 per cent degradation in 90 min by solar sono-photocatalysis
Zinc Oxide, Graphen Oxide Nanoparticles combination	Pharmaceutical wastewater obtained after three cycles from cleaning production lines of one batch of levofloxacin (Egypt, 2020)	Levofloxacin[112]	99.2 per cent for 50 µg/ml levofloxacin, and 99.6 per cent for 400 µg/ml levofloxacin
Photo-fenton oxidation ($H2O2/Fe^{2+}$/UV system)	Real wastewater from a petrochemical manufacture (Iran, 2018)	Meropenem and ceftriaxone[113]	99 and 96.2 per cent were observed for respectively meropenem and ceftriaxone
Ozonation and photo-catalysis	Pharmaceutical wastewater from local production plant which produces antibiotics, particularly fluoroquinolones (Pakistan, 2019)	Ciprofloxacin[114]	Ozonation: degradation rate faster under basic conditions with 98.7 per cent degradation; Photocatalysis: 100 per cent degradation within 30 min under optimized TiO_2 dose
A lab-scale simulation reactor, including up-flow anaerobic sludge bed (UASB), anoxic-oxic tank and four separate advanced oxidation processes (AOPs) i.e., UV, Ozonation, Fenton, and Fenton/UV	Wastewater collected from a real pharmaceutical factory that mainly produced tetracyclines (China, 2019)	18 antibiotics of which oxytetracycline and tetracycline were dominant; accounted for 96.8 per cent all detected antimicrobials*[115]	All antibiotics were fully eliminated through the reactor during 180 d-operation (removal efficiency > 99.8 per cent); UASB provided the greatest contribution (85.8 ± 16.1 per cent) for the removal of 18 antibiotics
Photocatalytic degradation by double-shelled $ZnSnO_3$ hollow cubes for efficient	Artificial pharmaceutical wastewater including ciprofloxacin, sulfamonomethoxine	Ciprofloxacin and sulfamonomethoxine[116]	85.9 per cent, 37.5 per cent
Adsorption and photocatalytic degradation using Activated Carbon based TiO_2 Composite (ACT-X)	Simulated pharmaceutical wastewater (Pakistan, 2023)	Ceftriaxone[117]	99.6 per cent photocatalytic degradation by ACT-4 photocatalyst; reusability up to five cycles with > 80 per cent photocatalytic degradation
Anaerobic membrane bioreactor	Wastewater collected from WWTP in a pharmaceutical company located in Hebei; generated mainly from product manufacturing and equipment cleaning process (China, 2018)	β-lactams antibiotics including amoxicillin, ceftriaxone, cefoperazone and ampicillin[118]	Highest removal efficiencies of amoxicillin, ceftriaxone, cefoperazone and ampicillin were 73.2 ± 4.3 per cent, 47.7 ± 2.2 per cent, 79.4 ± 4.1 per cent and 34.6 ± 3.3 per cent, respectively
Multiple draft tubes airlift loop membrane bioreactor (Mt-ALMBR)	Synthetic wastewater containing ampicillin (China, 2020)	Ampicillin[119]	63.2 ± 5.6 per cent at 7°C

Technology	Sample type (Country, Year of study)	Antibiotic(s)	Removal efficiency
Anoxic-oxic (A^2O), membrane bioreactor (MBR) and conventional activated sludge (CAS) systems	Wastewaters from different treatment points of two STPs and two pharmaceutical manufactories (PMFs) (China, 2021)	37 antibiotics belonging to four different classes of fluoroquinolones, macrolides, sulfonamides, and tetracyclines[120] **	Overall removal efficiency: 133.6–100 per cent at the STPs, and 142.8–100 per cent at the PMFs. Fluoroquinolones eliminated up to 100 per cent from raw influents of STPs and PMFs; >90 per cent removal efficiencies achieved for sulphonamides at PMFs. MBR system exhibited best performance compared to A^2O and CAS systems for removing majority of the detected antibiotics ; elimination rates of 33.4–100 per cent

*The 18 antibiotics include six sulfonamides (sulfamethoxazole, sulfachlorpyridazinesulfadiazine, sulfadimidine, sulfadimethoxine, and trimethoprim,), three quinolones (ciprofloxacin, enrofloxacin, and ofloxacin,), four tetracyclines (tetracycline, oxytetracycline, doxycycline, and chlortetracycline,), three macrolides (erythromycin, roxithromycin, and tylosin,), and two β-lactams (ampicillin, cephalexin); **The 37 antibiotics included: six tetracyclines (chlortetracycline, demecycline, metacycline, minocycline (MCL), oxytetracycline, tetracycline), thirteen sulphonamides (sulfamoxole, sulfadiazine, sulfamethoxypyridazine, sulfamethazine, sulfamethoxazole, sulfathiazole, sulfapyridine, sulfamerazine , sulfachlorpyridazine, sulfaquinoxaline, sulfadimethoxine, sulfisoxazole, sulfisomidine), five macrolides (clarithromycin, erythromycin, leucomycin, roxithromycin, tylosin), thirteen fluoroquinolones (cinoxacin, ciprofloxacin, danofloxaci), enoxacin, enrofloxacin, lomefloxacin, norfloxacin, ofloxacin, pefloxacin, sarafloxacin, nalidixic acid, oxolinic acid, pipemdic acid).

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Antibiotics are proving to be increasingly ineffective when it comes to treating bacterial infections. The growing public health crisis of antimicrobial resistance is silent but can be deafening. Among others, discharge from manufacturing companies that contain antibiotics can increase the risk of the development and spread of antibiotic resistance. Antibiotic manufacturing is often therefore referred to as a 'hotspot' for effective action.

This report presents how the global momentum is gradually building up to address the issue of antibiotic pollution. It also details out the antibiotic manufacturing scenario in India and the role it plays in global antibiotic supply chain. The report also captures the Indian policy and regulatory framework to control antibiotic pollution as well as the waste management practices that the antibiotic manufacturing companies claim to adopt.

In the end, the report provides a holistic view of the action required to be taken by different stakeholders to contain antibiotic pollution from manufacturing. Expectations from the Indian pharmaceutical industry to lead this change are growing. An effective and timely action can make a big change.

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