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# The Limit of Limits: India's Hurdles in Regulating Antimicrobial Pollution

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# Introduction

In late 2019, India's government introduced draft legislation that would have made it the first country in the world to limit the amount of antibiotics in waste released from pharmaceutical manufacturing plants into surrounding waterways. Twenty months later, following extensive commentary and argument on the proposed regulation from different viewpoints across multiple continents, any mention of limits had vanished from the final published rule.

In this CIDRAP-ASP report, we analyze the events surrounding the proposal and eventual removal of the limits, describing the issue of antibiotic pollution in India within the larger context of pharmaceutical demand and outsourcing of manufacture from high-income countries (HICs), the role of India as a competitive and necessary source of pharmaceuticals during the COVID-19 pandemic, criticisms raised about the antibiotic waste limits from diverse viewpoints and interests, and potential next steps for ensuring that the issue of environmental pollution remains in the foreground of all discussion about antibiotic innovation and manufacture.

# The Scope of Antimicrobial Pollution in India

The manufacture of active pharmaceutical ingredients (APIs)—the substances in medicines that produce a pharmacological effect—is the primary source of environmental antibiotic contamination. APIs are usually produced in bulk drug manufacturing sites, where unnecessary byproducts of the process are released as wastewater (ReAct 2020).

Approximately 100,000 tons of pharmaceuticals, including antibiotics, are used around the world every year, and manufacturing hubs in India are responsible for providing 20,000 tons of this immense global demand (Mohan 2020). At least 40 companies have API manufacturing plants in India, and the export of pharmaceuticals contributes approximately $20 billion USD to the Indian economy (Chatterjee 2020). The Indian government has exhibited strong support for the country's role as a hub for pharmaceutical manufacture and has encouraged, in recent years, a greater focus on API manufacture in India to reduce reliance on Chinese API imports (Mohan 2020).

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Large bulk drug manufacturing sites in India include the Patancheru-Bollaram Industrial Development Area in Telangana state, the Baddi Industrial Area on the border of Himachal Pradesh and Haryana states, and the SIPCOT Industrial Complex in Tamil Nadu state (Mohan 2020). To give an idea of scale, the Patancheru-Bollaram area hosts infrastructure for more than 30 companies, which together daily need to dispose of thousands of tons of pharmaceutical waste (Davies 2017). For more information and lists of

companies making APIs and finished antimicrobial medicines in India, please see the maps and lists in the Center for Disease Dynamics, Economics & Policy's 2017 "Scoping Report on Antimicrobial Resistance in India."

Monitoring of antibiotic residues and drug-resistant bacteria in waterways surrounding Indian industrial sites has increased in recent years, driven by attention from journalists and environmental policymakers. In 2019, the National Green Tribunal (NGT) found that all 90 bacterial strains isolated from the Musi River near pharmaceutical manufacturing sites in Hyderabad were multidrug-resistant, and several were extensively drug-resistant (Mohan 2020).

Similarly, in 2020, the India-based Veterans Forum for Transparency in Public Life presented findings to the NGT on ciprofloxacin levels that were more than 1,500 times the safe limit in the Sirsa and Sutlej rivers near the Baddi Industrial Area (Singh 2021). Because fluoroquinolones do not degrade quickly like many other antibiotics, their presence in waterways is particularly concerning (Taneja and Sharma 2019). The ciprofloxacin levels were confirmed by the Himachal Pradesh Pollution Control Board, yet local officials also noted that the common effluent treatment plant in the Baddi Industrial Area was incapable of treating antimicrobial runoff. In response to the receipt of these data, the NGT urged India's government to direct national pollution control officials to develop ways of monitoring the effluents discharged by pharmaceutical factories (Press Trust of India 2019, Singh 2021).

Several pharmaceutical manufacturers with factories in India (eg, NGB Laboratories, Centrient Pharmaceuticals, GlaxoSmithKline, Aurobindo Pharma) are members of the AMR Industry Alliance, a private-sector pharmaceutical industry group established to provide sustainable solutions to antimicrobial resistance (AMR), and have committed to "zero liquid discharge (ZLD)," a practice that recycles and treats manufacturing wastewater with the goal of minimizing pollutants that are discharged into nearby waterways (Singh 2021).

# The History of Antimicrobial Pollution Control in India

Though regulations affecting pharmaceutical manufacture—a key player in India's economic growth—are subject to the priorities of national and local governments, India has made steady progress over the past decade in demanding management of antibiotic residues in the environment. Recently, India's national government has taken steps to manage antibiotic use in animal agriculture, including a ban on the use of colistin in fish and livestock and the introduction of limits for antibiotic residues in meat, fish, and dairy products (Banerjee 2020, Kannan 2019, US Department of Agriculture Foreign Agricultural Service 2018).

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Partnerships with international governments and organizations have also played a recent role in bringing greater accountability from pharmaceutical companies operating in India. In summer 2020, the British High Commission New Delhi announced £8 million (about $10.3 million USD) in funding for surveillance projects that aim to clarify links between AMR in India and waste from antimicrobial manufacturing (British High Commission New Delhi 2020). About a year later, in August 2021, the UN Environment Programme announced that it will work collaboratively with the Indian Council of Medical Research to hold consultation and outreach activities that inform a stronger focus on the environment in national and state AMR strategies (UN Environment Programme 2021).

In 2021, researchers from the Indian Institute of Technology published a 2-year study of pharmaceutical waste in the Kaveri (often anglicized as

Cauvery) River, which runs across Karnataka and Tamil Nadu states in southern India and is used extensively for agricultural irrigation. The study found the presence of ciprofloxacin in the river, along with the presence of heavy metals that may select for AMR. Ciprofloxacin levels varied significantly with seasons, with higher concentrations observed at the beginning of winter over the course of the study. Long-term studies like this one can help to better understand the distribution and concentration of antimicrobial levels in rivers, especially because the Karnataka State Pollution Control Board tests river samples typically only four times per year (Renganathan et al 2021).

In addition to long-term research, efforts to find an even-keeled approach to pharmaceutical industry operations, national economic strength, and human and environmental health are under way in India. In fall 2020, Anita Kotwani, PhD, and Jyoti Joshi, MD, argued for a "smart regulation" approach to the issue, in which the engagement of people who are affected by AMR and pharmaceutical pollution drives change through social pressure, rather than regulation (Kotwani and Joshi 2020).

Another approach—the Responsible Antibiotics Manufacturing Platform—is led by the Stockholm International Water Institute and operates under the premise that accountability for mitigating antibiotic pollution must be enabled by innovation in technology and policy, robust data, and demand from the general public (Stockholm International Water Institute).

# A Proposal to Limit Antimicrobials in Pharmaceutical Wastewater

In December 2019, India's Union Ministry of Environment, Forest and Climate Change introduced a draft notification of proposed legislation —"Environment (Protection) Amendment Rules, 2019"—which established limits for 121 antimicrobials as measured in the treated effluent or sludge from a Bulk Drug and Formulation manufacturing site or a Common Effluent Treatment Plant and also required incineration for sludge containing antimicrobial residues (India Ministry of Environment, Forestry and Climate Change 2019).

The rules represented the result of India's complex history of efforts to improve pharmaceutical companies' accountability for environmental pollution and lower the harms caused by AMR in the country, while also ensuring the stability of pharmaceutical supply chains and the country's growing economy. The proposed limits also came on the heels of increased attention to antimicrobial pollution in Indian waterways surrounding drug manufacturing sites, partly due to investigations and communications campaigns led by the Bureau of Investigative Journalism, the Centre for Science and Environment in New Delhi, and the Stockholm International Water Institute.

> The draft rules would have made India the first nation in the world to introduce limits for antimicrobial concentrations in pharmaceutical waste, and, of note, the rules ensured that residues were measured before entering waterways.

Substantial commentary followed the release of the draft legislation, which entered a policy and economic environment made more unpredictable by the beginning of the COVID-19 pandemic. Much of the commentary hailed the possibility of India becoming the first country in the world to impose limits on antimicrobial waste and the perception of India as a hotbed of AMR,

although little attention was given to the practical nature of enforcing the limits and the pressure on India's government to balance environmental and economic health, international business alliances, and supply-chain demands during a pandemic.

In August 2021, India published the final notification of "Environment (Protection) Second Amendment Rules, 2021." All mention of antimicrobial limits in pharmaceutical effluent had been removed from the document, and the rules simply state that all effluents be classified as hazardous waste. In response, numerous commentaries expressed disappointment, although it remains hard to understand the events of the 20 months between the introduction of the limits and their ultimate disappearance from the final rules (Gaon Connection 2021, India Ministry of Environment, Forestry and Climate Change 2021).

# Criticisms, Issues, and Challenges with the Proposed Limits

## 1 | Basis and Infrastructure for the Limits and Conformity to Global Targets

Following the publication of the proposed rules, the Indian Drug Manufacturers Association (IDMA) argued to the Central Pollution Control Board that (1) the target antibiotic concentrations permitted by the regulations were lower than global targets set forth by the AMR Industry Alliance and (2) that pharmaceutical manufacturers using zero-liquid-discharge processes to treat wastewater in-house should be exempt from the rules. A lack of monitoring for ZLD compliance, however, makes it difficult to say whether or how much wastewater is being recycled within factories (Wasley et al 2020).

When commenting on the issue, representatives of the AMR Industry Alliance noted that its global targets, which were published in September 2018, are based on the risk of AMR attributable to concentrations of APIs in waterways, highlighting that a consideration of how the waterway might dilute pharmaceutical effluent (eg, a fast-flowing river would dilute effluent faster than a lake) did not inform the proposed Indian limits (AMR Industry Alliance 2018, Davies 2020). An important facet of India's proposed rules—the fact that they apply to antibiotic levels measured before discharge into rivers or lakes—was often excluded from criticism, which was, as in the case of the AMR Industry Alliance argument, often premised on antibiotic concentrations measured within waterways. Similarly, none of the laboratories participating in India's Antimicrobial Resistance and Surveillance Network are currently able to test for AMR in pharmaceutical discharge, making the point of applying global targets to pharmaceutical waste entering waterways somewhat moot (Mohan 2020).

An associated critique of the proposed antibiotic limits is that they are not only lower than global targets set by the AMR Industry Alliance, but that they are lower than antibiotic concentrations measured in treated sewage (Davies 2020). In its communications with national authorities, IDMA also referred to the limits as "arbitrarily" low and set "with no scientific

rationale." (Wasley et al 2020) While little public information about the process of developing the limits is available, it is important to reiterate that the limits are intended to apply to measurements before discharge into the environment and before dilution by water, making it reasonable that they would be lower than measurements taken after wastewater has entered the environment. Similarly, when measurements tend to be taken on the environmental presence of antibiotic runoff, the lack of data on residue actually discharged from a factory into water makes it difficult to determine whether or not a limit before discharge is excessively low.

Although India hosts numerous API manufacturers, the diversity of factories making antibiotic components means that national regulations on effluent discharge applied across the board may not address the problem. Aside from factories that make APIs, manufacturing sites also may make finalized drug (also known as finished dosage form) products or generic medicines that require more attention to manufacture than to development. Additionally, the mix of small, medium, and large pharmaceutical companies operating in India requires more discussion among industry professionals, scientists, and policymakers at the global and national levels about how environmental regulations can address variation in how different factories operate and how they contribute to medical supply chain resilience.

## 2 | Economic Challenges and the COVID-19 Pandemic

The IDMA also argued that, by imposing the limits on pharmaceutical manufacturers, the government would make it difficult for companies to operate in India, limit the availability of affordable medications, prompt the loss of API manufacturing business to China, and weaken the global pharmaceutical supply chain during a pandemic (Vishnoi 2021) when health supply chains were threatened and vaccine nationalism threatened global health security. The argument is not unreasonable: India experienced extreme shortages of the antifungal drug amphotericin B in 2021 during pandemic-related outbreaks of mucormycosis, and a global shortage of polymyxin antibiotics has led to hospitals changing treatment programs for bacterial infections (Khan 2021, Arun 2021, Chaiben 2022). Pandemic-related antimicrobial shortages did not appear out of nowhere, however; most countries struggle with occasional shortages, and a lack of access to necessary medicines is most acutely experienced in low- and middle-income countries (LMICs).

Conversations surrounding the rules in India also brought up the fact that HICs do not impose stringent limits on antibiotic effluent in wastewater, highlighting the importance of the pharmaceutical industry in India's economic development (Vishnoi 2021). While many lauded the limits as beneficial for human and environmental health, India's health ministry noted the need to balance manufacturer accountability with the feasibility of imposing the legislation prior to removing the antibiotic limits from the proposed rules. Officials cited the difficulty of monitoring and enforcing compliance from companies that would possibly withdraw from the country rather than invest in wastewater treatment (Banerjee 2020).

Pharmaceutical manufacture in India requires an even-keeled approach that accounts for the needs and perspectives of industry, science, healthcare, government, and the people most likely to be affected by antimicrobial pollution. Rather than create situations in which companies increase pollution globally by spreading out sites of manufacture, it may be wiser to focus on the hot spots of antimicrobial contamination with technological improvements, pollution mitigation, and monitoring and regulatory systems that account for the differences in pharmaceutical company size and operations.

# Intention and Importance of the Proposed Rules

## 1 | Limits and Not Targets

By setting limits that apply to the effluent itself, rather than targets that apply to effluent isolated from nearby waterways, the Indian Ministry of Environment, Forest and Climate Change aimed to reduce the amount of antibiotics released into waterways. The divergence from global targets set by the AMR Industry Alliance reflected this key difference and also raised discussion around the possibility that pharmaceutical companies may lack the motivation, enforcement mechanisms, and environmental expertise to establish their own limits or targets (Wasley et al 2020, ReAct 2020).

It is also important to address the fact that effluents from healthcare and agricultural settings often include concentrations of antimicrobials, and that hospital effluent has been associated with the spread of antimicrobial-resistant pathogens in India (CDDEP 2017). More studies are needed to inform how, when, and why regulations at the national level should target industry manufacturers, hospitals, farms, and other polluters. Well-informed regulations would ideally be based on long-term studies that account for the difference in antimicrobial API versus finished-product manufacturers and small and large companies, as well as monitor antimicrobial distribution, concentrations, and seasonality in waterways.

## 2 | Industry Responsibility

The rules would have applied equally to all pharmaceutical companies with factories in India, even those that claim to use zero-liquid-discharge processes. Rather than continue to address the problem of pharmaceutical pollution by measuring its effect on human health or passing the responsibility to pollution control agencies, the proposed limits would theoretically force companies to manage the issue before it causes environmental damage.

## 3 The Need for Accessible, Transparent Pharmaceutical Pollution Data

Conversations around how the proposed limits were determined highlighted the fact that very little data are available upon which to premise regulation. The 2020 AMR Benchmark report published by the Access to Medicine Foundation revealed that none of the world's largest 17 antibiotic producers provide data on the levels of antibiotic residue discharged in wastewater (Access to Medicine Foundation 2020). Whether the limits were truly arbitrary or were based on the best-available information at the time, their inclusion in the draft rules created an environment in which regulators realized that baseline information on environmental AMR is necessary for decision-making and legislative progress (Shetty 2021).

## 4 Improvements in Monitoring Infrastructure

The proposed rules served to question how they might be enforced and highlighted significant gaps in the ability to implement environmental contamination laws, not only in India but across the world. Part of the IDMA's argument against passing the antibiotic limits involved the possibility that factories would not comply, either because there was no way to enforce compliance or because they lacked the technology to measure antibiotic residues and clean wastewater before discharge (Mohan 2020, Banerjee 2020). And, as mentioned previously, India's AMR surveillance labs are not equipped to monitor industrial wastewater.

Regulatory capacity strengthening for regular and long-term monitoring in the environment is important, and, in a world where the United Nations Environment Programme has just joined the Tripartite at the global level to address AMR, much more work on surveillance capacity and data-informed regulation needs to be done at the global level rather than at the country level only (World Organisation for Animal Health 2022).

# Antimicrobial Pollution and Accountability

Much of the global support for the draft rules and the disappointment at their removal from the final legislation focused on the extensive pharmaceutical production and permissive regulatory environment in India, while ignoring the demand for antibiotics and lax business accountability in HICs that enable the very practices they decry.

Many policy groups in European nations voiced their support of the limits to the Indian national government, although the EU currently does not impose environmental standards on medicines produced for sale in Europe, nor does it require or incentivize surveillance or greater transparency on antibiotic effluent and other pollutants from European pharmaceutical companies operating in India (Swedwatch and the Swedish Society for Nature Conservation 2020).

In a commentary for Dalhousie University, Jee In Kim, MSc, says, "AMR is a global problem, yet the burden is not distributed equally across the globe. Even if Europe and North American-centric AMR research communities were to present the most ground-breaking findings, the root of the problems in production is still somewhere else in the world, where the perpetuation of AMR depends on the HICs' product demand." (Kim 2021)

> As the role of the environment in AMR selection and transmission becomes more apparent—not to mention the links between drug resistance and climate change—an "us and them" mindset that views antimicrobials as anything other than a public good should be abandoned sooner rather than later.

HICs profit from basing pharmaceutical factories in LMICs that are unable to monitor for AMR in the environment or regulate contaminants in waterways. National governments—those in which the factories are based and those importing medicines made abroad—are likely the only bodies with power to

demand accountability, monitoring mechanisms, and interventions that prioritize human and environmental health from pharmaceutical manufacturers. Yet, in the case of LMICs, national leaders are often hamstrung by a reliance on international pharmaceutical companies for economic growth. HICs with manufacturing hubs in lower-income nations have a responsibility to contribute to strengthening regulatory capacity in regions that host factories and provide technological support for improved and multisectoral environmental AMR solutions.

Swedish policy groups, notably Swedwatch and the Swedish Society for Nature Conservation, have advocated for the implementation of environmental standards for pharmaceutical companies importing medicines to the EU, also touting the importance of making antibiotic and API supply chain information publicly available. Because the steps of pharmaceutical manufacture are so fragmented globally, however, the national government of the country that hosts factories has the most power—and often, the most economic risk—to impose environmental regulations.

At the heart of the issue—and at the core of the hopeful, condemnatory, and disappointed conversations surrounding the limits—is language that positions India as a hotbed of uncontrolled AMR and a threat to the health of hapless visitors. While a view of people from poorer nations as hosting dangerous germs or bringing them along as they travel or flee is not uncommon in public health, it remains a way to dismiss responsibility for the role that HICs bear in allowing the burden of a problem to exist largely elsewhere and to care about it only when it inevitably threatens to spread. As the role of the environment in AMR selection and transmission becomes more apparent—not to mention the links between drug resistance and climate change—an "us and them" mindset that views antimicrobials as anything other than a public good should be abandoned sooner rather than later.

Whether the antibiotic limits were intended to be passed into law or proposed to prompt some remedy-seeking movement for India's pharmaceutical wastewater pollution problem, the draft legislation—a global first in a developing country (when no such legislation exists in HICs)—displays India's potential leadership prowess in environmental health and mitigation of antimicrobial pollution. The research, policymaking, and advocacy involved in furthering work toward limiting antimicrobial pollution in the environment must be supported rather than shunned as a failure, as it began global conversations that brought the environmental and human health costs of antibiotic manufacture to light.

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