Stakeholder Consultation

Containing antibiotic pollution from manufacturing to reduce the risk of AMR
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Growing global momentum to address antibiotic pollution from manufacturing and India’s role in global antibiotic supply chain
Growing recognition that manufacturing discharge adds to the risk of AMR and needs to be addressed
Call for countries, pharmaceutical industries and scientific community

To improve the management of discharges into the environment

Focus on:
- strengthened governance and oversight
- improved surveillance and data availability
- improved discharge management
- research and development
Environmental aspects of manufacturing in WHO Good Manufacturing Practices (GMP), 2020

• WHO adopted the ‘Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance’

• Made recommendations for
  – antibiotic API and FPP manufactures for self-audit
  – inspectors carrying GMP inspection about the application of waste and environment-related clauses mentioned in different WHO GMP texts

• Outlined expectations from manufacturers (not mandatory)
  – related to risk assessment, environmental protection, effluent treatment, and adequate documentation for different aspects of waste management
Group of Seven (G7) nations focusses on manufacturing discharge, 2021

- **Recognized need for**
  - **Standards** for antibiotics in manufacturing discharge
  - **Procurement** (purchasing/reimbursing) of antibiotics manufactured as per these standards
  - Accelerating the adoption of changes in WHO GMP
  - Using manufacturing and environmental standard related guiding principles for more sustainable antimicrobial drug development
EU plans to source medicines based on green manufacturing

- Notes 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.

- Considers the possibility of using procurement policy to encourage greener pharmaceutical design and manufacturing, and encourage action in third countries.

- Calls upon public buyers to design smart and innovative procurement procedures, by improving aspects such as ‘green production’.
Environmental criteria in procurement of pharmaceutical products: country level initiatives (examples)

- **Sweden** plans to procure and incentivize environmentally sustainable antibiotics through
  - national initiative on ‘environmental premium’
  - a national level sustainability criteria for medicines
  - an antibiotic procurement criterion in Region Stockholm
- Other EU countries like **Denmark** and certain non-EU countries such as **Norway and Iceland** have also taken initiatives in this direction

**Steps to get the environmental premium**

- **Pharmaceutical company to apply to Swedish MPA for environmental premium**
- **Swedish MPA informs Swedish E-Health agency about which product fulfils the criteria for an environmental premium**
- **The Swedish E-Health agency calculates and pays the environmental premium to the companies**

- **Company can apply to TLV with a reduced price of the product which increases the chance that their product will be selected as product-of-the-month leading to increased sale**
- **TLV publish the list of the product-of-the-month and informs the Swedish E-Health agency**
- **Sales in pharmacies of medicines within the product-of-the-month system**

The environmental premium is a fixed amount per sold package of products in the period of the month system. Intended to stimulate the companies to lower their price.
Industry response to the AMR crisis

The AMR Industry Alliance

- >100 members; 16 from R&D pharma sector, 9 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
- So far, they have come up with:
  - **Science-based PNEC targets for risk assessment**
  - Annual progress reports
  - Antibiotic Manufacturing Standard, 2022: guidance to manufacturers to manufacture antibiotics responsibly, to minimize AMR risk (authorization/license/permit compliance, characterization of wastewater discharges, quantification and assessment of antibiotic discharges, control of routine discharges and non-routine discharges)
  - Certification scheme in collaboration with the BSI, 2023
PNEC targets for risk assessment based on which discharge targets are to be set

- **PNEC (predicted no-effect concentration)**: 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
  - **PNEC-MIC values**: intended to be protective of resistance promotion
  - **PNEC-ENV values**: intended to be protective of ecological species

- **PNEC targets**: First science-based PNEC targets by Alliance in 2018 to guide environmental risk assessments.
  - If both PNEC-MIC and PNEC-ENV values available, then lower value is adopted as a target
  - If an antibiotic is not listed in the studies, a value of a similar antibiotic is made the target
  - If no data, default PNEC of 0.05 μg/l was used.

- PNEC-ENV and PNEC-MIC values adopted from scientific published literature. The updated 2023 PNEC targets for risk assessment are provided for 128 antimicrobials.

- **Discharge target** can be derived using these PNECs and site-specific parameters (≤ PNEC targets)

- Antibiotic concentration in the wastewater discharge should not increase the risk of AMR. Predicted environmental concentration (PEC)<Predicted no effect concentration (PNEC) [PEC/PNEC = Risk Quotient (RQ) and RQ<1]

- Alliance urges member companies to work towards achieving these targets at the receiving water body

  MIC (minimum inhibitory concentration), is the lowest concentration of an antibiotic that inhibits the growth of a given strain of bacteria
India as part of the global antibiotic supply chain
Antibiotic import and export in 2021-2022

- **Import and export of antibiotics**
  - Import (21.9%)
  - Export (78.1%)
  - Total: 1,15,911 MT

- **Antibiotics imported as APIs and FPPs**
  - APIs (97.6%)
  - FPPs (2.4%)

- **Antibiotics exported as APIs and FPPs**
  - APIs (28.1%)
  - FPPs (71.9%)
  - Total: 83,291 MT

- **Antibiotic API exports (Sulphonamides and penicillins)**
  - Europe: 14.0%
  - North America: 3.2%
  - Latin America: 17.5%
  - Africa: 42.6%
  - Asia: 22.5%

- **Antibiotic formulations exported (14 select antibiotics)**
  - Europe: 11.4%
  - North America: 8.8%
  - Latin America: 5.5%
  - Africa: 44.0%

Penicillin and cephalosporin (45%)

Source: Export Import data bank (Annual), Department of Commerce, Govt. of India
India’s antibiotic manufacturing sector, policies and practices related to waste management and pollution regulation
Antibiotic manufacturing hubs

25 locations/hubs across nine states in India
Policy framework on manufacturing and waste management

- **Good Manufacturing Practice requirements**
  - GMP mentioned under Schedule M of Drugs and Cosmetics Act. Regarding waste management, GMP requirements suggests compliance with the local and/or national laws like:
    - Sewage and effluents (solid, liquid and gas) as per the requirements of the Environment Pollution Control Board,
    - Biomedical waste as per the BioMedical Waste (Management and Handling) Rules, 1996
    - Rejected drugs as per guidance of central and state laws

- **Categorization of pharmaceutical industry based on pollution-causing potential (based on PI score):**
  - API/bulk drug manufacturers under red category, formulation industry under orange category; CETPs under red category

- **Discharge standards for pharmaceutical manufacturing effluents in India**
  - Effluent standards for bulk drug and formulation units, as per Environment (Protection) Second Amendment Rules, 2021
  - Compulsory parameters like pH, BOD, COD, TSS; additional parameters like phosphates, sulphides, zinc
  - None for antibiotic residues

- **Discharge standards for CETPs**
  - For treated effluent, standards for inland surface water, land for irrigation and into the sea
  - General (pH, BOD, COD, TSS, FDS) and specific standard (temperature, oil, etc) different for all three; no standards for antibiotics
  - SPCB to prescribe the inlet quality standard
Standards with regard to antibiotics
Limits for antibiotics in manufacturing effluents in India

- **January 2020:** Draft 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 (by MoEFCC)
  - limits for 121 antibiotics
  - were applicable at the final outlet of ETP of the bulk and formulation industry, as well as CETPs connected to it
  - ZLD to be considered when treated effluent used in process or utilities (boiler/cooling tower etc.), not in gardening/horticulture
  - Sludge containing antibiotic residues to be incinerated

- **August 2021:** draft notified
  - limiting values for antibiotic residues were dropped
  - mentioned 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
Case in NGT and Supreme Court

- **2020:** Petition filed 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 in 2020

- **Interim orders by NGT**
  - Constitution of Joint Committee (comprising MoEFCC, CPCB, Himachal Pradesh PCB, District Magistrate, Solan) to look into the matter
  - CPCB to develop guidelines for monitoring APIs

- **April 2022: Final verdict by NGT**
  - Proposed standards as per 2020 MoEFCC draft notification to be followed by all concerned
  - CPCB Guidelines on Monitoring Mechanism for API residues to be abided
    - requirements for the analysis of antibiotic residues
    - Frequency of monitoring as well as duties of SPCBs and Pollution Control Committees (PCCs)
    - provided recommendations like process control, waste water source categorization, frequent sampling, etc

- **May 2022:** Following final verdict, MoEFCC filed **review petition against verdict which was dismissed**

- **October 2022:** the case was moved to the Supreme Court
- **As on July 2023,** hearing in process; a stay on order of NGT has been placed
Key findings from the final report of the Joint Committee

• Himachal Pradesh PCB (HPPCB) monitored 210 pharmaceutical industries in Baddi-Barotiwala area, of which 111 were manufacturing antibiotics.
  • Of the 111, 37 were non-compliant with regards to the limits for discharge parameters prescribed for discharging into CETP.

• 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.
Based on responses from 14 antibiotic manufacturers (four large and 10 small-and medium-scale):

- **Waste management approaches adopted by companies depend upon multiple factors**
  - nature, scale of operations; type of antibiotic manufactured, quantity of waste generated; available infrastructure, efficiency and effectiveness of technology; legal requirements; awareness and preference; commitments made

- **Large scale companies:** focus on **process control measures** (mass balance, spill control, mopping instead of floor washing etc.), in addition to resource-intensive waste management technologies/approaches like **zero liquid discharge (ZLD) technology**; Few companies also mentioned use of advanced methods like **membrane bioreactors**.

- For **small and medium pharmaceutical manufacturers**, most commonly used approach is to send the **primary treated waste** to the CETPs

- In some cases, the manufacturers have utilized a **combination of technologies**. For example, **deactivation with sodium hydroxide/sodium hypochlorite** along with primary treatment before sending wastewater to the CETP; reverse osmosis (RO) instead of installing the entire ZLD infrastructure.
Common effluent treatment plants in antibiotic manufacturing hubs

• Out of the 25 antibiotic manufacturing hubs across nine states
  • 16 hubs across six states have a total of 35 CETPs (varying capacities: 0.5–55 MLD)
  • 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

• Out of 35 CETPs
  • Only four have wastewater recovery systems; One in Telangana, two in Ahmedabad, one in Karnataka.
Case studies: CETPs

- Baddi CETP and JETL, Telangana show two different approaches of wastewater management being used

- Baddi CETP segregates wastewater based on the type of industry and treats it separately; type of effluent received is likely to have a lower TDS since it caters to formulation producers

- JETL distributes waste streams irrespective of industry into high and low TDS and treats it according to the TDS; effluents being received can have both high and low TDS owing to API manufacturers dominating the region.

- JETL has modified its infrastructure to include MEE, ATFD and RO; Baddi CETP, uses cost-effective approach for treating pharmaceutical effluent twice

- Costing approach is also different for the two; Baddi CETP has an internal formula to decide on the cost per KL; In JETL costing based on standardized values of TDS (different for low as well high TDS effluents) and COD.
Way ahead: what Indian policymakers, regulators, and pharmaceutical industry should do to address the issue
It is clear that...

- **Consensus to act on manufacturing discharge is growing** - global scientific community and governance structures (current level of evidence enough to act)
- **AMR Industry Alliance response is in the right direction but lacks scale** (needs wider adoption by big global companies and deep in supplier networks)
- **Huge expectations from the Indian pharmaceutical industry** (integral part of global antibiotic supply chain)
- **No standards to directly address antibiotics in manufacturing discharge** (despite high pollution-causing potential)
- **The antibiotic limits proposed in the draft Indian standard are based on science** (on PNECs as AMR industry alliance standards; incorporates reduction efficiency of ETP/CETP)
- **Companies adopt a varying set of waste management approaches based on several factors**
- **Most CETPs in antibiotic hubs rely on conventional treatment approaches** and often lack advanced treatment or wastewater recovery systems
- **There is evidence that antibiotic pollution is a reality**
- **Waste management approaches are best when adopted based on specific factors of a company/CETP**
Why action is needed?

- **Action on antibiotics in manufacturing discharge can be very effective** (one of the drivers, should not get de-prioritized; relatively less complicated - local presence at high concentration, limited stakeholders with capacity. **Hotspot – possibility for effective action**)

- **Effective action is linked to several challenges, which need to be systematically addressed** (Challenge - maintaining antibiotic supply chains, access to cheap antibiotics; cost of action is to be understood in light of cost of burden of AMR; cost of action to be shared by all stakeholders – e.g., government support to upgrade CETPs)

- **India’s pharmaceutical industry stands to gain in the long-term, if it timely initiates and supports effective action.** Global momentum to procure antibiotics manufactured sustainably to put pressure on Indian exports; containing antibiotics in discharge, linked with their long-term usefulness; a big reason to keep them effective (benefitting companies and people both)

- **India will be hugely benefitted from an effective action** (opportunity to invest in preventing future health and economic crisis. Antibiotics not only save human lives but also livelihood of a significant population involved in livestock and fisheries)
The way ahead (1/4)

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

1. **Invest in creating awareness and building capacity among stakeholders.** Such as:
   - State pollution control boards and antibiotic manufacturing industry
   - Process control, waste management, new technologies, documentation, data sharing

2. **Data development to support policy formulation, implementation and monitoring.** Such as through a coordinated initiative – CPCB and SPCBs, CDSCO, Dept. of pharmaceuticals to:
   - Identify manufacturers of antibiotics, locations; kind of antibiotics manufactured and their quantities
   - Quantity of wastewater; waste management approaches used; treatment at in-house ETPs
   - Capacities and capabilities of CETPs, their locations and connectivity with manufacturing units

3. **Regular surveillance and monitoring of manufacturing units and CETPs.** CPCB Guidelines on the Monitoring Mechanism for API residues should be referred. Regular surveillance by SPCBs with help from CPCBs
   - Detect levels of antibiotics in samples from the ETP of manufacturing unit and CETPs; share results publically
   - Inspect and ensure that wastewater is not discharged unlawfully without treatment
   - Check if the desired segregation and process control measures are followed
   - Conduct audits on the documentation on waste stream analysis, mass balance etc.
4. **Strengthening laboratory capacity to support surveillance efforts.** Includes:
   - Improving laboratory infrastructure at the state-level
   - Developing necessary standard operating procedures, validating methods etc.

5. **Upgrade and enable capacity and capability of CETPs to address antibiotics**
   - All small-and medium-scale antibiotic manufacturing units across the country to be connected to CETPs
   - Based on gap assessment of CETPs, their capacity to be enhanced to degrade antibiotic residues
   - Advanced treatment systems should be considered and invested upon, if needed.

6. **Support small-and medium-scale companies in managing antibiotic discharges**
   - A nation-wide assessment to understand the gaps in the capabilities in treating the antibiotics
   - Small companies manufacturing antibiotics can be supported to manage their waste
   - Support to ensure - effective primary treatment, low-cost approaches/technologies, appropriate segregation and process control measures.
   - Incentive-based and/or financial support programme to help upgrade and build capacity

7. **Formulate and implement a long-term research agenda**
7. Notify legal limits for antibiotics in discharge from manufacturing units and CETPs

- There are limits for other hazardous toxic chemicals/heavy metals in pharmaceutical and CETP discharges; antibiotics should also have a legal limit

- **One option, MoEFCC notifies the limiting values it proposed in its draft of 2020. If considered too stringent, PNEC targets by the pharmaceutical industry can be considered.**
  - Considered feasible to test and achieve, PNEC targets are accepted among the global scientific community; are suitable for a harmonized approach; can facilitate trade/supply of antibiotics

- **These targets should be applied to the treated effluent from the manufacturing units’ ETP and CETPs connected to it, instead of receiving water body.**
  - 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.
  - 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.
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. Can be instrumental; Small-and medium-scale companies appear to focus less on it. All companies should build in-house capacity, upgrade and invest in process control systems

10. Build in-house capacity and upgrade waste treatment systems aimed at eliminating antibiotics in manufacturing discharge.
Upgrade should be based on the 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.
• 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.
• Facilitate policy development such as related to notification of limiting values/discharge targets
• Should be open to sharing all relevant data with regulatory agencies.
Thank you!
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