

Tackling AMR at antibiotic API Production Sites

Pilot Study of AOK Baden-Württemberg, the Rheinisch-Westfälisches Institut für Wasserforschung (IWW) and with the Support of the German Environment Agency (UBA)

Key Findings on environmental Sustainability
in Antibiotics' Production

German Statutory Health Insurances (SHI) – discount contracts

- Contract pharmaceuticals: Preferably to be dispensed by pharmacies
- Contracts tendered according to public procurement law
- Voluntariness: SHI reimbursement based on list prices if no offer is submitted

Antibiotic active pharmaceutical ingredients (API): Use of insured funds for audits worldwide

- Health insurance funds are for insured health purposes solely but:

AMR as a global issue builds a bridge between AMR sources in distant countries and the needs of 27 million AOK-insured people

Granting Advantages in Tenders to tackle AMR

Offers regarding antibiotic APIs in a tendering procedures will get a 6% bonus on the discount offered under following conditions:

- AOK publishes within the tender the predicted no effect concentration values (PNECs) for antibiotic APIs that must not be exceeded in wastewater of production sites
- The bidder as a pharmaceutical company assures that all API producers agree upon compliance with PNECs published and to allow audits on site
- At a second stage API producers agree upon PNEC compliance and audits accordingly
- Audits are conducted on site by an independent reputable scientific institute (IWW) with short lead time, samples are analysed using RP high performance liquid chromatography in Germany

Executing Audits on API Production Sites



Audits include a presentation of water treatment technology used at the production site, a joint inspection of the site and finally sampling at the end of the water treatment and in the neighbouring environment

Acceptance within generic antibiotics market

	Tender		
	AOK Z1 (06/2021 - 05/2023)	AOK XXV (02/2022 - 05/2025)	AOK XXVII (06/2023 - 05/2025)
Number of bidders applying for antibiotic API bonus criterion	7	9	17
Number of bidders applying for antibiotic API bonus criterion and awarded contract	3	5	13 (19 production sites)
Number of API under contract with bonus criterion applied	3	4	11

Executing Audits on API Production Sites



First Results (Extract): Audits performed for AOK

API	Location	PNEC [$\mu\text{g/l}$]*	Result [$\mu\text{g/l}$]
Ciprofloxacin	India	0.089	creek leaving facility: 16 934
Clarithromycin	India	0.13	RO exhaust: 22.5
Clindamycin	China	0.04	Rain water basin: 184 502
Levofloxacin	India	0.25	RO Outlet: 7.34 Rain water collection unit: 0.37 creek after passing site: 8.48 creek at an effluent spot within the site's wall: 90
Azithromycin	India	0.03	Environment, rainwater spillway > 500
Cefaclor	Europe	0.94	Production stopped 10 days before visit; no Cefaclor found; environment sampling: 50 other API with 9 other antibiotic API found exceeding PNECs by 100% up to 33000 %
Amoxicillin+ Clavulanic acid	Europe	0.05	No Amoxicillin found, 2 other antibiotic API found exceeding their PNECs by about 300%

*derived from the German Environment Agency (UBA)

Audits on API Production Sites: Consequences



First Results

Advantages

- Rising awareness for environmental aspects of API production
- Initiating improvements to comply with contractually agreed environmental standards (PNECs, emission limit values)

Some Measures taken by API producers

- Consultation of external experts to gain knowledge
- Improving equipment (Reverse Osmosis-Checkups, scaling up pH-treatment devices etc.)
- Involving a specialised EU laboratory for analytics, sampling on a regular basis

Limits of a bonus-based contractual approach

- Pharmaceutical companies and API-Producers agree voluntarily
- Investments on API-production sites vs. economical benefit of API-Producers (Germany's market share on the global antibiotics market is approx. 4%)
- SHI: Funds are used for environmental protection instead for health needs directly

Impressions: Sampling Sites



AOK Baden-Württemberg

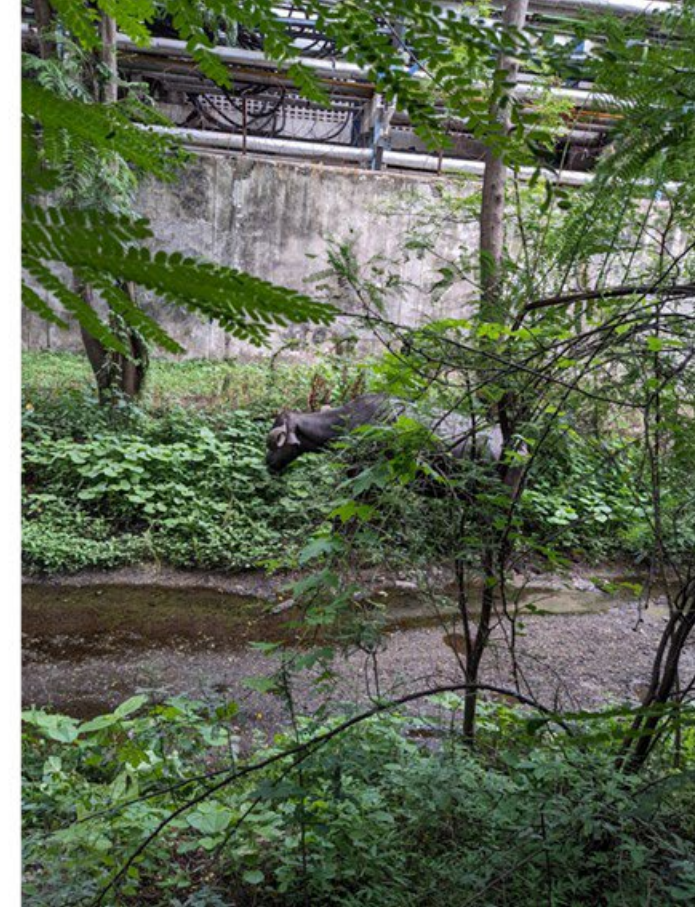


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Impressions: Sampling Sites



Impressions: Sampling Sites



Impressions: Sampling Sites



Further need for action

Production sites within EU and in third countries can be hot spots for environmental pollution with antibiotics and may contribute to AMR. In order to safeguard public health and amid the One Health policy the following actions aiming at limiting emissions at API production sites are needed:

- Environmental criteria need to be strengthened within the EU marketing authorisation framework for antibiotics and other API that pose a risk for the environment
- Interventions needed regarding production sites within EU – but even more so within third countries

Further need for action

- In order to tackle AMR there is an urgent need for legally binding emission limits for production sites of antibiotics and for mandatory and uniform EU auditing requirements
 - to ensure API production conditions, which do not contribute to the development of AMR nor harm the environment
 - and as a lever to create a level playing field for EU API producing competitors

Obligation and control instead of voluntariness and self commitments!

Thank You kindly for Your attention.