Combating Antimicrobial Resistance: A Manufacturing Perspective

Steve Brooks
VP, EHS Pfizer Inc
& Chair, Environmental Work Group of the AMR Industry Alliance
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Affordable, accessible, antibiotics are essential to public health, bring huge societal benefits

Industry supply chain for established antibiotics is global with significant footprint in emerging markets including India and China.

Reports of environmental pollution from drug manufacturing plants notably in some emerging markets.

Key reports (e.g., O’Neill) assert linkage to AMR, state better control of manufacturing effluent needed

Continued academic, media, investor reports highlight high levels of antimicrobials in environmental samples, e.g., India.

Recognized concern for many stakeholders, including industry.

Leading companies and industry organization publicly committed to address the risk of AMR, including reducing risks of environmental impact from manufacturing antibiotics and established Environmental Work group of the AMR Industry Alliance

..so lets take a look at ANTIMICROBIALS in the Environment and Manufacturing
Sources of Antimicrobials in the Environment

MANUFACTURING
One Potential Source of Many

- Livestock Treatments
- Treatment of Companion Animals
- Storage of Manure and Slurry
- Inappropriate Disposals of Used Containers and Unused Medicine
- Aquaculture Treatments
- Wastewater Treatment
- Manufacturing Process
- Receiving Water
- Soil
- Manure / Slurry Spreading

Boxall (2004)
Active Pharmaceutical Ingredient (API) may be found in manufacturing solid waste and waste water:

Solid waste should be managed to prevent soil and ground water contamination
- Poor waste practices have been reported in proximity to some Indian manufacturing sites

Waste water - Effective controls needed to minimize API concentration in receiving water
- Varying controls adopted across manufacturing sites
- Both “safe” discharge concentrations and means to determine waste water concentrations needed to ensure effectiveness of controls.
- Science continues / needs to evolve, e.g., role and significance of other co-selective agents (e.g., metals, biocides, cleaning agents etc.)

Let’s look at the industry response AMR and creation of the “Environmental Work Group” to address manufacturing environmental commitments
Industry Declaration on Combating Antimicrobial Resistance

The AMR Declaration was Released on January 21, 2016 at the World Economic Forum in Davos, Switzerland. It Calls on Key Stakeholders to Take Collective Action in Addressing the AMR Problem. Governments Should Work to:

1. Create a sustainable and predictable market for new antibiotics
2. Improve financial and access-related predictability
3. Global coordination / local action

The full text of the AMR Declaration can be found here

The Signatories to the Declaration Commit to:

1. Work to reduce the development on antimicrobial resistance
   • Including “measures to reduce environmental pollution”
2. Invest in R&D to meet public health needs with new innovative diagnostics & treatments
3. Improve access to high-quality antibiotics and ensuring that new ones are available to all

Signatories to the Declaration include 87 bio / pharmaceutical companies, 16 diagnostic development companies, and 13 industry associations.
The Industry Roadmap for Progress on Combating Antimicrobial Resistance
Signed by 13 Companies in September 2016

Implement Measures to Reduce Environmental Impact from Production of Antibiotics
- Review supply chains, establish discharge framework and targets

Support education campaigns, examine promotional activities, support surveillance activities, minimize uncontrolled access

Commit to Antibiotics only being used in Patients who need them

Partner with Stakeholders to Improve Access to Antibiotics, Diagnostics and Vaccines
- Address bottlenecks and strengthen market sustainability, develop new business models, address counterfeit and low quality medicines

Advance R&D through New Collaborations and Incentives
- Support new open collaborations between industry and public researchers, partner to establish new incentive models, support new clinical trial networks
WE SUPPORT MEASURES TO REDUCE ENVIRONMENTAL IMPACT FROM PRODUCTION OF ANTIBIOTICS, AND WILL:

- Review our own manufacturing and supply chains to assess good practice in controlling releases of antibiotics into the environment.

- Establish common framework for managing antibiotic discharge, and start to apply it across our own manufacturing and supply chain by 2018.

- Work with stakeholders to develop a practical mechanism to transparently demonstrate that our supply chains meet the standards in the framework.

- Work with independent technical experts to establish science-driven, risk-based targets for discharge concentrations for antibiotics and good practice methods to reduce environmental impact of manufacturing discharges, by 2020.

We support calls for the establishment of a high-level coordinating mechanism to provide global leadership, mobilize resources, set goals and measure progress towards them.
AMR Industry Alliance Environmental Work Group

Through outreach (e.g., with other industry groups / stakeholders) we hope to influence many more companies to take appropriate action (e.g., through adoption of work products)

Formed to drive progress in meeting common environmental commitments in the Roadmap and (through the Alliance) to report progress

EHS leaders from 13 Roadmap signatory companies

Will consult with stakeholders to ensure approach is robust and transparent

Science sub team developing common approach to establishing science-driven, risk-based targets for discharge concentrations

Each company has taken and is taking action to assess and enhance own supply chain

Drafting an environmental management framework / standards

Understanding each others current environmental assessment programs

LET’S LOOK AT WHAT TO EXPECT OF MANUFACTURERS
Antibiotic resistance is ancient

Vanessa M. O’Conor1,2*, Christine E. Kling3,4*, Lindsay Kohan3,5, Marita Meade1,3, Wilson W. L. Sung2, Cayten Schwartz2, Duean Fowles2, Grant Zabel2, Pauline Callaham2, Hugh Delapaz2,6, G. Brian Gilding2, Henrik L. Petersen5,6,8 & Grant D. Wright1,2

The discovery of antibiotics more than 70 years ago initiated a period of drug innovation and implementation in human and animal health and agriculture. These discoveries were tempered in all cases by the emergence of resistant microbes. This history has been interpreted to mean that antibiotic resistance in pathogenic bacteria is a modern phenomenon. This view is refuted by the fact that collections of microbes that produce the antibiotic enzyme are highly susceptible to antibiotics. Here, we report targeted metagenomic analyses of rigorously authenticated ancient DNA from 16,000-year-old Beringia permafrost sediments and the identification of a highly divergent collection of gene encoding resistance to β-lactams, tetracyclines and glycopeptide antibiotics. Structure-function studies on the complete norresistance element Yank confirmed its similarity to modern variants. These results show conclusively that antibiotic resistance is a natural phenomenon that predates the modern selective pressure of clinical antibiotic use.

Recent studies of modern environmental and human commensal microbial genomes have revealed a much larger concentration of antibiotic resistance genes than has been previously recognized. In addition, metagenomic studies have revealed diverse homologs of known resistance genes broadly distributed across environmental organisms. This widespread dissemination of antibiotic resistance elements is consistent with a hypothesis of contemporary emergence and animal origin, which is consistent with a recent history of resistance, recent evolution of the origins of natural product antibiotics range from 2 Gya to 60 Mgy ago suggesting that resistance should be similarly old. Previous publications claim to have cultured resistant bacteria from 16,000 years ago. The results outline additional (see Supplementary Information).

To determine whether contemporary resistance elements are modern or whether they originated before our use of antibiotics, we analyzed DNA sequences recovered from Late Pleistocene permafrost sediments. The samples were collected out of Dawson City, Yukon, at the Iron Creek–BDC site (Fig. 1). Prominent forms of ground ice (ice wedges and ice rafts) are preserved in the deposits, immediately overlain by a distinct volcanic ash layer. The tephe has been dated at several sites in the area to about 28,000 radiocarbon years ago (28,000 years BP) and about 16,000 calendar years ago. The cryostratigraphic context is similar to other sites in the area preserving a low permafrost and indicates that the permafrost has not thawed since the time of deposition (Supplementary Information). In the absence of data lacking the site menu.

**What to Expect of Manufacturers**

1. First as a reminder - AMR in the environment is ancient and pre-dates industrial scale use of antibiotics

2. Environmental releases of antibiotic residues from manufacturing plants can be controlled and confirmed through a mass balance approach.

3. Monitoring of manufacturing waste streams may be helpful in limited cases with targeted analytical verification.

4. Benefits of extensive antibiotic monitoring or antimicrobial resistance gene (ARG) monitoring in the context of manufacturing is not clear at this time:
   - Clear links are being established between ARG prevalence and environmental concentrations of antibiotics
   - The relationship of environmental presence (antibiotics and ARGs) and the spread of AMR and adverse clinical outcomes in patient due to resistant infectious disease is less clear and requires further investigation.

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**Letters**

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Summary

Manufacturing is one potential source of antibiotics in the environment.

The Environmental Work Group of the AMR Industry Alliance is developing an environmental framework, standards and science-driven, risk-based targets for discharge concentrations.

Consultation and communication with relevant experts / stakeholders is important to ensure robust work product.

Wide spread adoption is key - innovators and generics - to reduce overall manufacturing contribution to antibiotics in the environment.