The Environmental Dimension of Antimicrobial Resistance: An Industry Perspective

Professor Jason Snape
UKRI – India Meeting - Delhi

16th May 2019
Issue to be addressed….

- Stakeholder concerns about antimicrobial resistance (AMR)
- Industry response
- Setting protection goals for environmental and human health
- Ongoing scientific and regulatory challenges
Stakeholder challenges: focus on drug production

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Type of drug</th>
<th>Range (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>Antibiotic-fluoroquinolone</td>
<td>28,000–31,000</td>
</tr>
<tr>
<td>Losartan</td>
<td>Angiotensin II receptor antagonist</td>
<td>2,400–2,500</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>H1-receptor antagonist</td>
<td>1,300–1,400</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>β1-adrenoreceptor antagonist</td>
<td>800–950</td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td>Antibiotic-fluoroquinolone (veterinary use)</td>
<td>780–900</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Serotonin reuptake inhibitor</td>
<td>770–840</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>Antibiotic-fluoroquinolone</td>
<td>390–420</td>
</tr>
<tr>
<td>Lomefloxacin</td>
<td>Antibiotic-fluoroquinolone</td>
<td>150–300</td>
</tr>
<tr>
<td>Enoxacin</td>
<td>Antibiotic-fluoroquinolone</td>
<td>150–300</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Antibiotic-fluoroquinolone</td>
<td>150–160</td>
</tr>
<tr>
<td>Ranitdin</td>
<td>H2-receptor antagonist</td>
<td>90–160</td>
</tr>
</tbody>
</table>

Pollution from drug manufacturing: review and perspectives

D.G. Joakim Larsson
Institute of Biomedicine, The Sahlgrenska Academy, The University of Gothenburg, Gothenburg, Sweden

Review

Cite this article: Larsson DG. 2014 Pollution from drug manufacturing: review and perspectives. Phil. Trans. R. Soc. B 369: 20130371.
http://dx.doi.org/10.1098/rstb.2013.0371

One contribution of 10 to a Theme Issue ‘Assessing risks and impacts of pharmaceuticals in the environment on wildlife and ecosystems’.
Stakeholder challenges: increased NGO Pressures
Stakeholder challenges: investor pressure
Stakeholder challenges: investor pressure

AMR: a major global health threat associated with pharmaceutical pollution

The World Health Organisation’s 2014 report on global surveillance of antimicrobial resistance revealed that “antibiotic resistance is no longer a prediction for the future; it is happening right now, across the world, and is putting at risk the ability to treat common infections in the community and hospitals.”

The WHO and other eminent global health experts warn that we are at the dawn of a “post-antibiotic era”, which will result in millions of fatalities every year. The UK’s Independent Review on AMR projects a death toll of 10 million people per annum by 2050 if resistance is left unchecked, with a cost of up to $100 trillion. This is a conservative estimate, which only takes into account part of the impact of AMR.

Rising resistance is taking a devastating toll on the Indian population, particularly the most vulnerable members of society. The first ‘State of the World’s Antibiotics’ report published by the Washington-based Center for Disease Dynamics, Economics and Policy (CDDEP) in 2015 noted that 58,000 newborn babies in India died in 2013 as a result of drug-resistant infections, while Indian drug resistance rates for several major pathogens is on the rise.

Key causes of antibiotic resistance are inappropriate use of antibiotics in humans and overuse in intensive animal farming. Another, often overlooked cause, is pollution resulting from the pharmaceutical manufacturing process itself.

AMR is viewed by experts as one of the major threats to human health emerging from pharmaceutical pollution. Indeed, a 2013 report by the European Agency for Health and Consumers notes that “Without any doubt, the development of AMR is by far the largest risk for humans of having medicinal products residues in the environment.”

As the AMR review stated in its watershed report on the environmental dimension of AMR at the end of 2015, pollution from the production of antibiotics “needs to be viewed as a straightforward issue of industrial pollution, and it is the responsibility of all actors in the supply chain to ensure that industrial waste is treated properly as a matter of good manufacturing practice.”
What do all these Stakeholders have in common?
What do all these Stakeholders have in common?
AZ Approach to API discharges

Managing Emissions of Active Pharmaceutical Ingredients from Manufacturing Facilities: An Environmental Quality Standard Approach

ABSTRACT
Active pharmaceutical ingredients (APIs) have been identified as one of the most critical areas for improving the sustainability of pharmaceutical production. This paper presents a new approach to risk assessing pharmaceutical emissions. The approach is based on the concept of environmental quality standards (EQS) and is designed to provide a framework for the assessment of environmental impacts of pharmaceutical production processes.

INTRODUCTION
The environmental impact of pharmaceutical production is significant and has become a major concern for the industry. The production of APIs is a complex process that involves the use of a wide range of chemicals, including solvents, catalysts, and reagents. These chemicals are used in the synthesis of APIs, which are then further processed to produce the final drug product. The production of APIs is a major source of environmental pollution, and there is a growing concern about the sustainability of the pharmaceutical industry.

Keywords: Active Pharmaceutical Ingredients (APIs); Environmental Quality Standards (EQS); Risk Assessment; Pharmaceutical Production.
Industry response: AMR Roadmap

The group of leading bio-pharma companies commit to:

1) **Reduce environmental impact from production of antibiotics**, including a review of the companies’ manufacturing and supply chains, establishing a common framework to assess and manage antibiotic discharge;

2) **Ensure Antibiotics are used only by those who need them**, via i.e. education programs, examination of the companies’ promotional activities, sharing of surveillance data, and reducing uncontrolled antibiotic purchase (OtC/Web);

3) **Improve access to current/future antibiotics and vaccines**, reduce the prevalence of substandard / counterfeit antibiotics by i.e. serialization; strengthen health systems and address access bottlenecks; establishing new business models that balance access needs, appropriate use, and adequate return

4) **Explore new opportunities for open collaborations between industry and the public sector** to address challenges in R&D of new antibiotics, vaccines and diagnostics, recognizing the value these bring to society.

On Sep 20, 2016:
13 Leading Bio-Pharma, including AZ, issued a UNGA Roadmap on AMR:

Among other commitments such as Excess Use, Access to Antibiotics, and New collaboration forms, the environmental impact of antibiotics manufacturing is given high priority.
Industry response: reducing production impacts

We support measures to reduce environmental impact from production of antibiotics, and will:

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

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

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

iv. 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.
Setting protection goals for antibiotics

• Environmental Risk Assessment Data
  • NOECs for activated sludge, algae (cyanobacteria), daphnia and fish
  • EC50 and LC50 data for algae (cyanobacteria), daphnia and fish

For antibiotics the OECD 201 algal growth inhibition study is usually conducted with cyanobacteria.
Setting protection goals for antibiotics

- Environmental Risk Assessment Data
  - NOECs for activated sludge, algae (cyanobacteria), daphnia and fish
  - EC50 and LC50 data for algae (cyanobacteria), daphnia and fish

NOEC – No observed effect concentration; PNEC – Predicted no effect concentration; EC – Effect concentration; LC – Lethal Concentration


Review article

Integrating human and environmental health in antibiotic risk assessment: A critical analysis of protection goals, species sensitivity and antimicrobial resistance

Gareth Le Page¹, Lina Gunnarsson², Jason Snape³, Charles R. Tyler⁴

¹ Bioscience, College of Life and Environmental Sciences, University of Exeter, Geoffrey Pope, Stocker Road, Exeter, Devon EX4 4QR, UK
² AstaLudens, Global Environment, Alderley Park, Macclesfield, Cheshire SK10 4TF, UK
³ School of Life Sciences, Gibbet Hill Campus, The University of Warwick, Coventry, CV4 7AL, UK

NOEC – No observed effect concentration; PNEC – Predicted no effect concentration; EC – Effect concentration; LC – Lethal Concentration
Setting protection goals for antibiotics

- But we only routinely test one cyanobacterial species
Setting protection goals: what other options exist?

- Levels of antimicrobial resistance genes (ARGs)
  - Treats the genetic determinants for resistance as pollutants (bacteria and naked DNA)

- Activity-based assessments
  - Range of US Food and Drug Administration (FDA) approved antibiotic residue tests/activity assays; many designed to screen milk (low sensitivity)

- Number of ceftaxime resistant E. coli
  - Looks to build upon existing bathing water standards for enterics by looking at resistant enteric component

- Minimum Selective Concentrations (MSCs)
  - Some data starting to appear for simple competition assays and some complex microbial communities
Setting protection goals for antibiotics

- Clinically relevant data
  - Bengtsson-Palme & Larsson (2016) PNEC(RT) for 111 antimicrobials
  - MIC data extracted from EUCAST database
  - Lowest 1% of MICs identified and corrected against number of species
  - Assessment factor of 10 applied to account for differences between MIC and MSC
- PNEC(RT) range from 8 ng/L to 64 μg/L
Setting protection goals for antibiotics

• Comparing NOEC from le Page et al (2017) with the adjusted MIC from Bengtsson-Palme and Larsson (2016)
COMMON ANTIBIOTIC MANUFACTURING FRAMEWORK

The Antimicrobial Resistance (AMR) Roadmap Companies recognize and understand concerns raised by stakeholders regarding the presence of pharmaceuticals in the environment (PIE). The major source of pharmaceuticals entering into the environment is via patient excretion following use of medicine that is taken to prevent, cure or alleviate a medical condition. A comparatively smaller contribution to PIE stems from emissions from industry during manufacture of the pharmaceuticals.¹

While the overall contribution of pharmaceutical manufacturing to PIE is relatively low, there is the potential for localized impacts to be created in cases where manufacturing emissions are inadequately managed. Ensuring the use of appropriate environmental risk management measures to adequately control manufacturing effluent emissions remains an important area of focus for the pharmaceutical industry and is an approach already in place in a number of companies.² We are aligned in our intent and are ready to build and share common practices.

Reports of active pharmaceutical ingredients (APIs) in water from pharmaceutical manufacturing indicate concentrations have reached potentially harmful levels when wastewater discharges are not sufficiently controlled at some facilities,³ highlighting the importance of effective control of API emissions from manufacturing, both in production of the API itself and its formulation into drug products for patient use.

Environmental regulations pertaining to wastewater discharges from manufacturing, already generally apply to pharmaceutical production. However, many socially and environmentally responsible companies go beyond compliance with the basic regulatory requirements for chemical manufacturers (e.g., control of pH, biological oxygen demand, chemical oxygen demand)⁴ and establish environmental protection goals to evaluate and reduce potential environmental risk from production of their products.

Currently, most programs focus on potential toxicity to aquatic species, upset to wastewater treatment plants or potential toxicity in human drinking water. Emission limits, specifically for preventing antimicrobial resistance, are currently under development. The AMR Roadmap signatories are committed to achieving this goal and are reliant on the evolving science as a means to arriving at a consistent methodology for these limits by 2020.

The Antibiotic Manufacturing Framework provides a methodology and set of minimum requirements needed to conduct a site risk evaluation of both macro and micro controls in our supply chains. Company expectations, including this Framework, will be communicated within the AMR Roadmap signatory companies and their supply chains.
Industry publishes antibiotic discharge targets

AMR Industry Alliance Antibiotic Discharge Targets

The AMR Industry Alliance brings together over 100 biotech, diagnostic, generic and research-based pharmaceutical companies around the shared goal of curbing antimicrobial resistance. In the world, Alliance companies are committed to contribute to and measure their efforts in fighting AMR across 4 key areas: research, appropriate use, access and manufacturing and the environment.

Earlier in 2018, AMR Alliance generic and research-based pharmaceutical companies agreed on a framework that promotes responsible antibiotic manufacturing. Last week, these companies took a further step by publishing the first list of discharge targets to guide environmental risk assessments for the manufacture of antibiotics. This publication is an
Ongoing challenges….

• Resistance in part provides an ecosystem service (adaptive and protective)

• Chemical standards at end of pipe don’t address:
  – Antibiotic residues leaving the patient (pre-WWTP and selection)
  – AMR genes/ resistant bacteria leaving the patient or WWTP
  – AMR genes/ resistant bacteria being enriched in WWTPs
  – The presence of co-selective agents in influents and treated effluents

• High antibiotic concentrations do not always indicate high levels of resistance (e.g. B-lactams)

• How do we mitigate risks from mycelia and biosolids in a cos effect environmentally conscious manner?
Ongoing challenges....

- Resistance and human health is not included in ERA
- ERA process for antibiotics is too weak
  - Reliant on algae/ cyanobacteria and does not protect many ecosystem services provided by bacteria
  - Not the most sensitive species of cyanobacteria is being used
- Cocktail/ combined exposure effects
- Challenge of co-selection issues associated with other chemicals (e.g. metals and biocides)
  - Pure focus on antibiotics might not manage AMR risks
Ongoing challenges….

• Current clinical surveillance strategies do not include environmental matrices – will it help anticipate future clinical challenges

• Relative risk of difference exposure routes, locally and globally

• What are safe levels of ARGs

• What technologies/ interventions are needed?

• Will society pay for responsibly sourced antibiotics? Can it afford not to?
Think holistically….

- Avoiding unnecessary use (animal or patient) will reduce environmental exposure from that use and from production
  - Diagnosis
  - Good hygiene and sanitation
  - Education and behaviour management

- But will this be enough to reduce the evolutionary and selective pressures??

RAPID DIAGNOSTICS WOULD REDUCE UNNECESSARY PRESCRIPTION

Out of 40m people who get given antibiotics for respiratory issues, annually in the US:

27m get antibiotics unnecessarily
13m who need antibiotics get them

Societal pressures are going to increase!

Population of Sweden
Don’t under-estimate the power of a PhD

One student and one paper

Changes EMA ERA Guideline

Basis for targets for Industry
• Dr Gareth Le Page
• Dr Lina Gunnarsson
• Dr Baz Verbruggen
• Dr Aimee Murray
• Isobel Stanton
• Prof Will Gaze
• Dr Lihong
• Prof Charles Tyler

Confidentiality Notice

This file is private and may contain confidential and proprietary information. If you have received this file in error, please notify us and remove it from your system and note that you must not copy, distribute or take any action in reliance on it. Any unauthorized use or disclosure of the contents of this file is not permitted and may be unlawful. AstraZeneca PLC, 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge, CB2 0AA, UK, T: +44(0)203 749 5000, www.astrazeneca.com