Antibiotic Manufacturers' Commitments: supporting measures to reduce concentrations of antibiotics in manufacturing waste discharges

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Pfizer Today:
A Leading Global Bio-Pharmaceutical Company

$52.5
BILLION
in revenue in 2017

58
MANUFACTURING
sites worldwide

MORE THAN
125
COUNTRIES
in which Pfizer sells products

MORE THAN
180
NEW R&D COLLABORATIONS
in 2017

MORE THAN
90,000
COLLEAGUES
around the world

Company data as of March 1, 2018

Strong investment in manufacturing excellence

More than
2.1B INVESTED IN U.S. MANUFACTURING SITES *OVER THE LAST 5 YEARS.*

We have 15 manufacturing facilities in 10 states and Puerto Rico.

More than
11K MANUFACTURING EMPLOYEES IN THE U.S.

Nearly
63K DIRECT AND INDIRECT JOBS

Environment, Health & Safety; logistics and supply chain; manufacturing and packaging; production; line operators; process engineers; chemists; and quality control professionals.

Manufacturing data as of January 2018

Global leader of anti-infective medicines

Working closely with the infectious disease community, we are committed to addressing AMR through:

Active Stewardship

Surveillance

Global Policy Leadership

Expanding Our Diverse Portfolio of Medicines and Vaccines

Responsible Manufacturing Practices

At the bottom left of this slide is an illustrative diagram of a manufacturing facility to accompany text that conveys Pfizer has invested $2.1B in our 15 U.S. based manufacturing sites over the past 5 years (as of January 2018) - these sites are located in 10 states and Puerto Rico.

To the right of this a diagram of a person, a magnifying glass, three connected hexagons (like a chemical structure) and a flask half filled with liquid. This accompanies text that conveys that Pfizer, employs more than11,000 people in the U.S. and supports nearly 63,000 direct and indirect jobs in a number of disciplines, for example, in Environment, Health & safety; logistics and supply chain; manufacturing and packaging; production; line operations; process engineers; chemists; and quality control professionals. The diagram is simply a way of showing that many of these job are technical in nature.

Finally, on the lower right hand side of the slide there are 5 small diagrams to illustrate 5 areas in which Pfizer is working closely with the infectious disease community to address AMR. These diagrams are:

- Hands holding a globe - to convey “active stewardship”
- A person holding part of the world on their shoulders with the world “ATLAS” at the top – to convey “surveillance”; “ATLAS” is Pfizer’s Innovative surveillance tool to help physicians better understand current resistance patterns.
- A globe to convey “global policy leadership”
- A needle and syringe and 3 tablets (i.e. medicine) – to convey “expanding our diverse portfolio of medicines and vaccines.”
- A manufacturing factory – to convey “responsible manufacturing practices”

AMR - Manufacturing Environmental Matters

- Affordable, accessible, antibiotics are essential to public health, bring huge societal benefits
- Industry supply chain for 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
- Academic, media, investor reports highlight high levels of antimicrobials in environmental samples, for example, in India
- Recognized concern for many stakeholders, including industry and calls for governments to act
- Several potential sources of antibiotics in the environment, manufacturing being one
- The AMR Industry Alliance is the life sciences industry response to the call for action on AMR, including manufacturing matters

Member of the Alliance Manufacturing group include:

Allergan

AstraZeneca

Centrient Pharmaceuticals

Cipla

GlaxoSmithKline

Johnson & Johnson

Merck & Co

Mylan

Pfizer

Roche

Sanofi

Shionogi

Teva

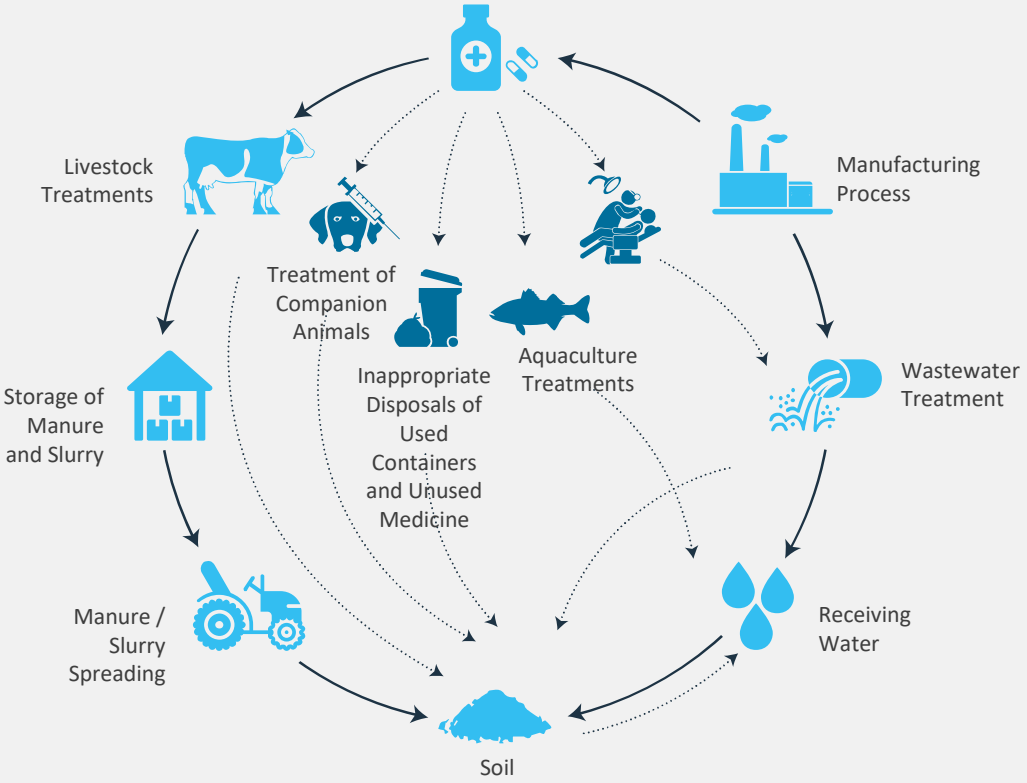
Novartis

Wockhardt

Sources of Antimicrobials in the Environment

MANUFACTURING

One Potential Source of Many



Boxall (2004)

There are a **number of pathways** that may lead to the presence of antibiotics in the environment.

- Nearly 80% of antibiotics are excreted by the body (human and animal), so runoff and improperly treated wastewater from hospitals, municipalities (including inadequate disposal of unused antibiotics), and farms (including aquaculture) contribute to antimicrobials in the environment [1].
- A comparatively smaller contribution stems from emissions from industry during manufacture of antibiotics, if manufacturing emissions are inadequately managed.

While the overall contribution from manufacturing discharges to antibiotics in the environment is likely small, locally it may be important; industry is aware of this and has committed to address manufacturing discharges.

[1] Heather Storteboom, Mazdak Arabi, Jessica G. Davis, Barbara Crimi, Amy Pruden. Tracking Antibiotic Resistance Genes in the South Platte River Basin Using Molecular Signatures of Urban, Agricultural, And Pristine Sources. Environmental Science & Technology, 2010; 44 (19): 7397 DOI: 10.1021/es101657s

Role of AMR Industry Alliance

The AMR Industry Alliance is commited to addressing its part. In 2016, we agreed to the following commitments on manufacturing and the environment:

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 a common framework for managing antibiotic discharge, building on existing work such as PSCI*, 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.*

**Pharmaceutical Supply Chain Initiative*

AMR Industry Alliance: Common Antibiotic Manufacturing Framework

- Companies in the biopharmaceutical industry, through the Alliance, have been actively implementing improvements within their manufacturing networks and based on experience gained:
- Developed and published **Common Antibiotic Manufacturing Framework** in early 2018
  - provides methodology and requirements to conduct risk evaluation of controls in place at Member sites and their suppliers' sites to effectively manage and *minimise potential release of antibiotics from manufacturing processes into the environment*
  - Is designed to ensure that manufacturing sites (and especially third party supplier sites) are, and are seen to be, managing antibiotic production and associated waste streams responsibly
  - Codifies what should be regarded as good practice
  - Adherence to framework will drive selection and use of appropriate suppliers

Framework Recognizes:

- There are concerns about concentration of antibiotics in the environment in proximity to some manufacturing locations
- Importance of effective control of manufacturing waste streams
- **Framework Provides:**
    - Methodology and minimum requirements needed to conduct a site risk evaluation of controls in place to ensure effective management of antibiotics waste streams at manufacturing sites

Framework Minimum Expectations

- Compliance with:
- Local laws and regulations
- Environmental permits
- Company standards, Codes of conduct
- Pharmaceutical Supply Chain Initiative's (PSCI) Pharmaceutical Industry Principles
- No untreated discharge of manufacturing waste containing antibiotic*

*with the potential to adversely affect human or environmental health

On site audits at least once every 5 years

- against defined protocol (e.g. own, PSCI)
- identification of any non-compliance/gaps
- monitor suppliers progress vs action plans to close
- determine on-going appropriateness of supplier efficacy
- Appropriate training is completed in line with industry best practice
- Exercise appropriate duty of care for all discharges and waste streams containing antibiotics
- Allow / facilitate audits as requested, develop and execute plans to address audit findings
- Follow-up conducted for assessments and audits conducted

Include (examples):

- Regulatory compliance assessment
- Operating permit compliance verification
- Focus on environmental management

- Facility tour – e.g. waste water treatment, waste storage, waste water collection, facility exterior

The Common Antibiotic Manufacturing Framework can be found: https://www.amrindustryalliance.org/wp-content/uploads/2018/02/AMR_Industry_Alliance_Manufacturing_Framework.pdf

AMR Industry Alliance Antibiotic Discharge Targets

- Recognizing, with a few specific exceptions, concentrations of active pharmaceutical ingredients (APIs), including antibiotics, in discharge from manufacturing sites or municipal wastewater treatment systems are generally not regulated (globally).
- The Alliance published (2018) an approach to establishing targets for antibiotic manufacturing referred to as **Predicted No-Effect Concentrations (PNECs)** for use in environmental risk assessment of antibiotics,
  - PNEC-Environment (PNEC-ENV) values are based on eco-toxicology data - intended to be protective of ecological species
  - PNEC-Minimum Inhibitory Concentration (PNEC-MIC) values are based on clinical data - intended to be protective of resistance promotion
- AMR Industry Alliance approach - target the lower of the two values (when available) for assessing manufacturing site discharges under a risk-based framework.
- Targets represent exceedingly low concentrations; meeting such targets may take time/add cost.

See slide notes for PNEC-ENV and PNEC-MIC references

- PNEC-Environment (PNEC-ENV) values are based on eco-toxicology data generated by Alliance member companies. These values are intended to be protective of ecological species and incorporate assessment factors consistent with standard environmental risk methodologies (Brandt et al., 2015 [2]; Le Page et al., 2017 [3]).
- The PNEC-Minimum Inhibitory Concentration (PNEC-MIC) values are based on the approach published in Bengtsson-Palme and Larsson (2016)[4] and are intended to be protective of resistance promotion.
- The AMR Industry Alliance recommendation is that companies target the lower of these two values (when available) for assessing manufacturing site discharges under a risk-based framework. This table will be updated periodically as new reliable and robust data become available.

The PNEC table can be found: https://www.amrindustryalliance.org/wp-content/uploads/2018/09/AMR_Industry_Alliance_List-of-Predicted-No-Effect-Concentrations-PNECs.pdf

[2] Brandt, et al., 2015. Ecotoxicological assessment of antibiotics: A call for improved consideration of microorganisms. Environment International, 85: 189-205.

[3] Le Page, et al., 2017. Integrating human and environmental health in antibiotic risk assessment: A critical analysis of protection goals, species sensitivity and antimicrobial resistance. Environment International, 109: 155-169.

[4] Bengtsson-Palme & Larsson, 2016. Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation, Environment International 86: 140–149.

Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000, Establishing a framework for Community action in the field of water policy. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32000L0060

AMR Industry Alliance – part of the AMR Solution

- Alliance members support measures to reduce concentrations of antibiotics **manufacturing waste discharges** in alignment with the:
  - Common Antibiotic Manufacturing Framework for responsible antibiotic manufacturing for generic and research-based pharmaceutical companies
  - List of Predicted No-effect Concentrations (PNECs), the first list of discharge targets to guide environmental risk assessments for the manufacture of antibiotics
- The Alliance will report (2020) progress in implementing the framework and meeting the discharge targets
- By working towards implementing the framework and meeting the targets across their supply chains, Alliance members will be taking steps to **further ensure antibiotic resistance selection pressures in the environment are minimized.**
- Wide spread adoption (beyond current Alliance membership) of the common antibiotic framework will be a **substantial step forward in minimizing the presence of pharmaceuticals in the local environment in proximity to manufacturing sites and will** minimize the risk of selective pressure on resistant organisms in the environment, thus helping to reduce the risk of the spread of antimicrobial resistance.

U.S. NAP Considerations

Understanding sources of AMR

- There are a number of pathways that may lead to the presence of antibiotics in the environment. There are reports that raise concerns of potential risk to human health and eco-systems. However, to date, there is no confirmed scientific link to human health risk from antibiotic discharge. Opportunities exist to:
  - Fund/stimulate further research to better understand the nature/extent of linkage between sources of environmental concentrations of ABs (or ARGs) and the development of clinical cases of antimicrobial resistance in the U.S.
  - Examine agriculture, hospital discharge, manufacturing effluent, human waste - armed with this knowledge, target policies to ensure greatest impact

Transition to enhanced waste management practices

Domestically

- Fund research into waste water treatment technologies e.g. of publically owned waste water treatment plants – to better address the risk of micro constituents including antibiotics
- Incentivize transition/upgrade to technologies that destroy/remove antibiotics e.g. consider eligibility under existing tax credits

Internationally

- To better ensure global health security , work with Governments (and global agencies) of countries that could "export" AMR as a result of gross environmental pollution to incentivize improved sanitation and development of robust waste management infrastructure and practices.

The Current UN NAP (2015) does not include environmental presence of antibiotics as a possible contributory cause of AMR. There is no reference to allegations of pollution in the antibiotic pharmaceutical supply chain with assertion that any such pollution may result in a spread of AMR.

The above recommendations would likely need to be made under a new area of a revised NAP addressing “the environment” as a key part of the “one health” approach.

Concluding Remarks

Industry is part of the solution.
The AMR Industry Alliance has developed a common manufacturing antibiotic manufacturing framework and published a list of antibiotic manufacturing discharge targets based on the best available science and 2 years ahead of our commitment to do so. Widespread adoption of the common antibiotic framework will be a substantial step forward in minimizing the presence of pharmaceuticals in the local environment in proximity to manufacturing sites and will minimize the risk of selective pressure on resistant organisms in the environment, thus reducing the risk of the spread of antimicrobial resistance.

Balancing access and increasing manufacturing expectations.
There is a paradox in the increasing downward pressure on antibiotic prices and increasing expectations regarding manufacturing practices. Tender mechanisms could help better support the security of supply by reflecting the cost of manufacturing using the techniques needed to reduce the risk of exacerbating anti-microbial resistance and therefore allowing for sustainably-made antibiotics

National Governments' engagement.
An important challenge is that the countries in which environmental pollution is of most concern are countries which have a large and growing chemical/pharmaceutical industry and generally less well developed environmental protections.

Support from International Organizations.
We urge global agencies to continue to engage governments, and provide support when appropriate, to facilitate implementation of National Action Plans in particular in countries with a key role to manage the risk of environmental pollution. Part of the solution may lie in greater partnerships between global organizations and industry, collaborating on common global goals.