WHITE PAPER

Manufacturing sustainable antibiotics for the future

Achieving a PNEC-compliant supply chain

CENTRIENT™ Pharmaceuticals

Reaching our goal of a clean antibiotics supply chain

Centrient meets the commitment to a PNEC-compliant supply chain for oral antibiotics

Centrient's commitment in the fight against antimicrobial resistance from manufacturing

In 2016, Centrient Pharmaceuticals ("Centrient") signed up to the UN General Assembly Roadmap on Antimicrobial Resistance, which was subsequently adopted by the private sector coalition, the AMR Industry Alliance. This pledge reflects our responsibility, as a leading provider of beta-lactam antibiotics to generic medicine marketers, to address the growing global health issue of antimicrobial resistance (AMR). As part of this commitment, Centrient pledged to reduce the environmental impact of the production of antibiotics, which is the journey that the company has been on for the past years. This goal has now been achieved in the form of PNEC compliance for the company's complete oral antibiotics product range.

Industry action against AMR from manufacturing

Research shows that commercial antibiotic manufacturers may be among the causes of antimicrobial resistance[1]. Without strong safeguards, antibiotic residues from manufacturing sites can reach water bodies through effluent and wastewater, spurring the development of resistance in bacteria already present in the environment.
The AMR Industry Alliance (of which Centrient Pharmaceuticals is a founding member), developed a Common Antibiotic Manufacturing Framework, which includes safe discharge targets for antibiotics known as Predicted No-Effect Concentration Targets (or PNECs). The member companies (who represent approximately 30% of the global human health antibiotic supply chain) have been on a journey to implement this standard at their own sites as well as at their suppliers' sites. In addition, efforts have been made to engage with companies who have not yet signed up to the AMR Industry Alliance, to help widen the uptake and impact of the standard across the entire industry.

Building on collaboration with others

In this paper, we outline the continued need for cohesive action to minimize the possible contribribution of antibiotic manufacturing to AMR. With a whole-value-chain approach, meaning pharmaceuticals manufacturers and buyers working together, an AMR-free manufacturing base is achievable. Our work involves partnering with authorities and healthcare institutions to improve standards and policies regarding antibiotics manufacturing and promote best practices. Moreover, this case study of successful cross-sector collaboration on AMR can be applied to a wider industry response to issues such as climate change and environmental degradation.

[1] 'Environmental Dimensions of Antimicrobial Resistance Summary for Policymakers' - United Nations www.unep.org

Centrient's achievement

Centrient meets the goal of ensuring a PNEC-compliant supply chain for its oral antibiotics – in line with the AMR Industry Alliance standards for best practice in managing manufacturing effluent

"Centrient Pharmaceuticals has been an industry leader in adopting the PNEC standard across its supply chain and encouraging peer companies to join the fight against AMR."

Steve Brooks, Manufacturing Working Group Chair, AMR Industry Alliance

Environmental contributors to AMR include manufacturing pollution

The release of antibiotics into the environment is thought to increase selection pressure leading to the emergence of antimicrobial resistance. A vast array of other contaminants, such as biocides and heavy metals, can combine to add further pressure on bacteria to become resistant. Once resistant bacteria are embedded in the environment, they spread through water and soil, potentially leading to exposure in humans and animals through food, water and air. Studies are ongoing to better understand the connection between antibiotics in the environment and the resistance in humans.

Main pathways of antibiotics into the environment

Adapted and modified from Boxall, A.B. (2004). The environmental side effects of medication. EMBO Reports, 5 (12), 1110-1116.

- Environmental causes are one of three main contributors to AMR, along with human and agricultural usage of antibiotics.
- Pharmaceutical plants can act as hotspots, releasing releasing relatively high concentrations of antibiotics into the environment – a particular concern in regions without adequate monitoring and wastewater management capacity.
- The AMR Industry Alliance developed the Common Antibiotic Manufacturing Framework and PNEC standards to establish safe discharge targets for antibiotics.

Why we must act now to contain AMR:

AMR caused **1.27 million deaths** in 2019, and antimicrobial-resistant infections played a role in **4.95 million deaths**

USD 60–100 trillion estimated global economic cost of AMR during 2015–2050

Source: 'Global burden of bacterial antimicrobial resistance in 2019' – The Lancet, January 2022
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02724-0/fulltext

Developing solutions to combat AMR from manufacturing

AMR Industry Alliance members created a framework to limit the impact of antibiotic emissions on the environment

The Common Antibiotic Manufacturing Framework

The AMR Industry Alliance has established a common framework for responsible antibiotic manufacturing. This establishes minimum expectations for business policies, practices and behaviours to minimise the release of antibiotics into the environment due to pharmaceutical production. The framework focuses on effective waste management and control and aims to prevent conditions that potentially drive the development and spread of resistant bacteria.

The PNECs: science-driven, risk-based targets

Effluents from manufacturing can lead to the release of antibiotic residues into the environment unless effective controls are in place. Even low antibiotic concentrations may trigger selection pressure for resistance among exposed bacteria. AMR Industry Alliance member companies assembled a committee of sector experts to review the available science and propose a method to establish 'Predicted No-Effect Concentrations' (PNECs) for antibiotics. This means antibiotic concentrations that, in the environment, would be unlikely to result in increased selection pressure on exposed bacteria. The proposed approach and a list of PNECs for approximately 120 antibiotics were published in a peer-reviewed article in 2019 and were adopted by the AMR Industry Alliance. They provide clear discharge targets for antibiotic manufacturing to guide environmental risk assessments of antibiotics.

What is PNEC?

The Predicted No-Effect Concentration (PNEC) is the concentration of an antibiotic in water at which there is unlikely to be a risk of adverse environmental effects or of antimicrobial resistance developing. The PNEC is estimated by dividing the lowest value for toxicity by the relevant assessment factor. Antibiotics manufacturers that meet the required PNEC discharge target are unlikely to cause an adverse environmental effect as a result of their effluents or to contribute to antimicrobial resistance.

"Manufacturing makes up a small proportion of antibiotic emissions. However, poorly controlled discharges can lead to high levels of active residues, resulting in hotspots of AMR. Better management of manufacturing emissions is critical in curbing the problem."

Alistair Boxall, Professor of Environmental Science, University of York, United Kingdom

[2] 'Making antibiotics responsibly; A common manufacturing framework to tackle antimicrobial resistance' – The AMR Industry Alliance, 2019 https://www.amrindustryalliance.org/wp-content/uploads/2019/11/Making-antibiotics-responsibly_A-common-manufacturing-framework-to-tackle-AMR.pdf

Moving from the Delvotest® to a new quantitative method

To reach stringent PNEC targets, Centrient invested in a new advanced testing methodology

Upgrading proprietary methodology

Centrient previously introduced an easy-to-use method to detect remaining antibiotic activity in our wastewater adapted from the Delvotest®, an approach for detecting antibiotic residue in milk. Rather than looking for specific molecules, the test takes a generic approach: it detects a broad spectrum of beta-lactam compounds including precursors and active ingredients, providing a result within a few hours. The test can detect an amount of antimicrobial activity (based on penicillin G) of 50 micrograms per litre (or 50 ppb).

Centrient performed this test at all our sites from 2016 until the introduction of the Common Antibiotic Manufacturing Framework and the PNECs.

New methodology implemented at Centrient sites

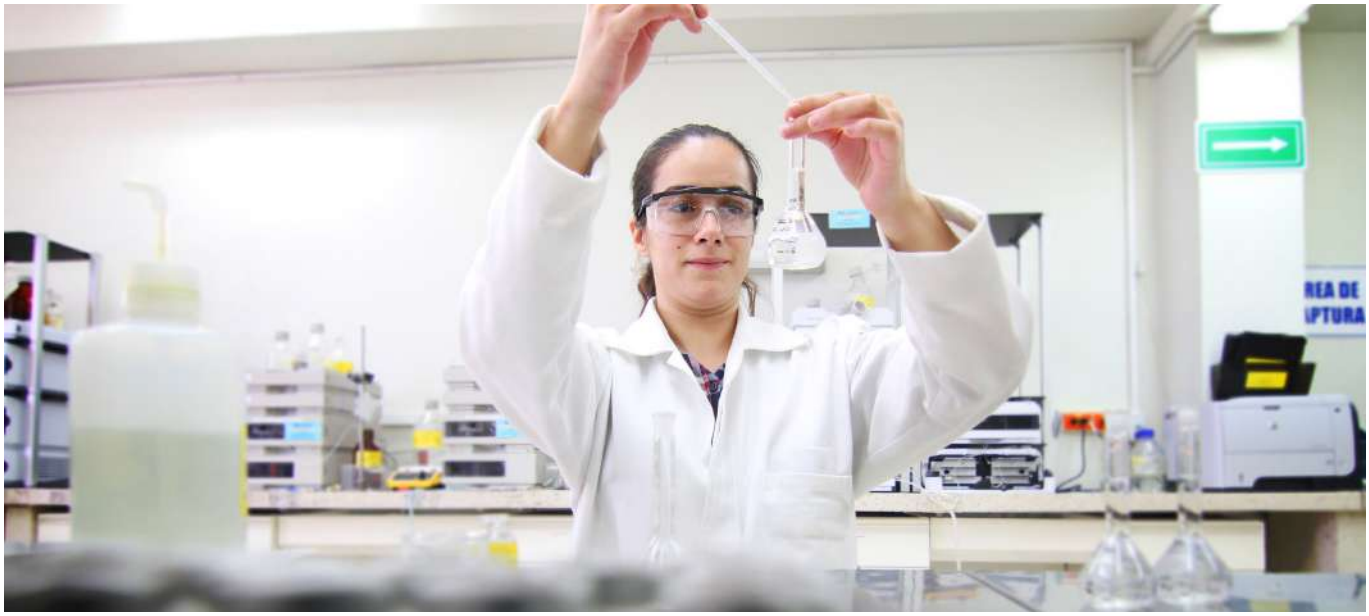
With the introduction of the AMR Industry Alliance's framework, Centrient strengthened its PNEC measurement programme through analytical method validation and improved sampling methods to drive compliance with PNEC targets. Furthermore, the company adapted and optimised a test based on the HPLC/MS method (US EPA Method 1694) for detecting residual chemicals. This method was validated by Centrient to test antibiotics in a highly sensitive and quantitative manner. Centrient's standard practice is for samples to be drawn every month and tested each quarter.

In 2019, the company confirmed PNEC compliance at its oral semi-synthetic penicillin manufacturing sites, which form the core of the company's portfolio. This was followed by the oral semi-synthetic cephalosporins range, for which compliance was achieved at the end of 2021. A recent acquisition (made in 2021) does not fall within the scope of Centrient's original AMR commitment and therefore is not yet considered. In 2022, this single new site will be assessed, and compliance will be announced in due course.

Centrient's route to supplier compliance with its AMR commitment

In 2019, Centrient launched Project PNEC with the objective of ensuring its supply chain was fully compliant. An AMR compliance assessment of suppliers was completed, and the results were communicated to the companies concerned, together with guidance on how to act on the findings. Centrient supported suppliers on both mass balance and analytical testing of the residual antibiotics in their wastewater streams.

In 2020, Centrient launched a second AMR assessment survey for suppliers, revised according to AMR Industry Alliance expectations on best practices to comply with Framework and PNEC target values. The results indicated a significant improvement in practices to minimise AMR risk, and in 2020 the company was able to confirm all its suppliers were 100% compliant with PNEC target values. Centrient requires suppliers to report quarterly regarding testing methods.



Partnering to ensure clean antibiotic supply chains

Buyers and manufacturers of antibiotics must commit to a PNEC-compliant supply chain

As the use of antibiotics and other pharmaceuticals expands worldwide, the value chain – from pharmaceutical buyers to industry regulators – recognises the growing need for responsible manufacturing. Environmental standards for antibiotics are increasingly included in national procurement processes, for example. The PNEC guidelines developed by the AMR Industry Alliance provide a clear science-based target to help manufacturers define safe limits for antibiotics effluents. Leading pharmaceutical players, from research-based companies to generic medicine manufacturers, are also using PNEC discharge targets as the basis for target-setting across their supply chains.

Approaches to antibiotics manufacturing increasingly considered in tender criteria

Procurement organisations are increasingly introducing tender criteria related to the way in which antibiotics are manufactured. In 2020, NHS England included criteria in antibiotic procurement for the first time related to environmental standards including "Demonstrated compliance, via independent assessment, with environmental standards relevant to the manufacture of antimicrobials throughout the supply chain, including compliance with discharge limits at owned and/or supplier manufacturing sites and external wastewater treatment plants". Following this, in 2021 German medical insurance provider AOK introduced a specific parameter on PNEC compliance that, if positively adhered to, would be beneficial to tendering companies. During the same year, the United Nations Development Program (UNDP) developed the Sustainable Procurement Index for Health, a structured set of questions and criteria for buyers to use in a procurement process which included PNEC compliance for antibiotics[3].

Additionally, countries including Norway and Sweden already include general environmental criteria for antibiotics in their procurement processes. While specific countries and organisations press ahead with various initiatives, the need remains for a common framework to help firmly embed responsible antibiotics-manufacturing approaches within the procurement process.

The need to harmonise procurement criteria for the clean manufacturing of antibiotics

Adopting a global common set of criteria for sustainable antibiotic manufacturing is essential to ensure a consistent standard and reduce the burden for all stakeholders involved. Working towards this goal is the Responsible Antibiotic Manufacturing Platform (RAMP), a partnership between the Stockholm International Water Institute (SIWI), the Swiss Agency for Development and industry partners such as Centrient Pharmaceuticals, GSK and Sandoz. RAMP aims to harmonise standards for clean antibiotic manufacturing and advocate for their adoption by procurement bodies worldwide.
Centrient and other partners call for procurement bodies to join the voluntary platform to ensure a consistent approach with the aim of facilitating the efforts required for reporting and verification.

[3] 'Sustainable Procurement Index for Health (SPIH) – United Nations Development Programme', October 2021 https://api.savinglivesustainably.org/documents/file/764e233134ffe62af43550927d10c2eb/full/hash

A blueprint for a more sustainable value chain

With the global pharmaceutical value chain working together to install and maintain PNEC standards, we can enable a future in which antibiotic manufacturing no longer directly contributes to AMR

However, strategies to limit AMR should also be considered within the broader context of current environmental concerns. After all, the human causes of climate change – i.e., the burning of fossil fuels and the emission of greenhouse gases – are intimately linked to population growth, urbanisation, and the increasing demands of consumers. These conditions, among others, are likely accelerators of antimicrobial resistance. In addition, a warming climate provides conditions that are more favourable to the development of AMR[4]. Such considerations reinforce the need for joined-up thinking to ensure the pharmaceutical industry responds in a coordinated, effective manner to the challenge of AMR and related environmental issues.

[4] 'Climate change and antibiotic resistance: a deadly combination' – Burnham JP., January 2021 https://journals.sagepub.com/doi/full/10.1177/2049936121991374

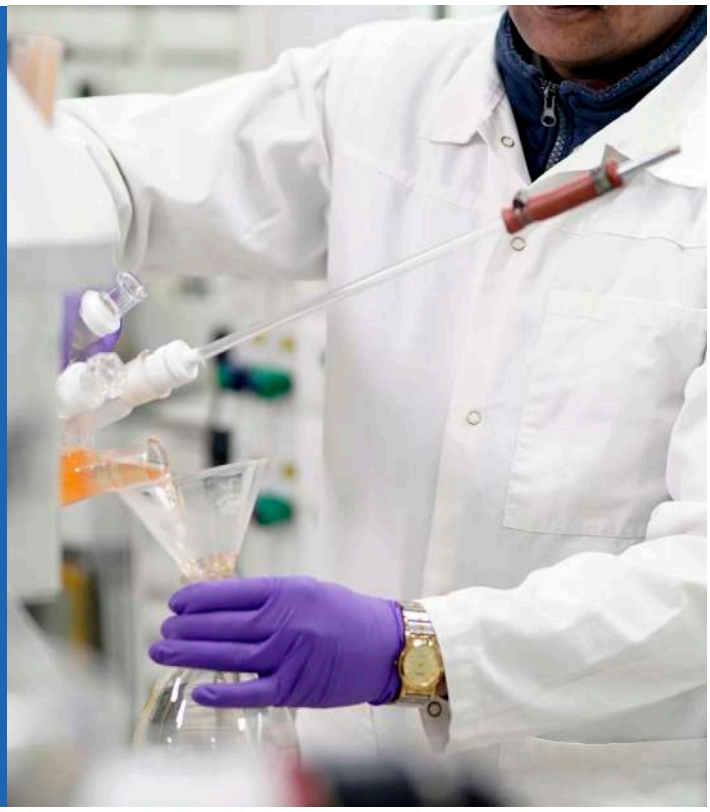
The pharmaceuticals industry's carbon footprint in figures:

+55% relative emissions intensity of the pharma sector versus the automotive sector 2013–2015

59% required reduction in the pharma sector's emissions intensity by 2025 (vs 2015 levels) to meet the Paris Agreement goals

<10% of pharmaceutical companies consistently reported direct and indirect GHG emissions during 2013–2015

Source: '2018 analysis of top-15 pharmaceutical companies by McMaster University' https://www.sciencedirect.com/science/article/abs/pii/S0959652618336084?via%3Dihub



A holistic approach to antibiotics manufacturing

Centrient is taking a holistic approach to tackling AMR and related environmental challenges such as climate change. A case in point is the company's ongoing investment in 'green' enzymatic production technology. This proprietary platform replaces the traditional 13-step antibiotics production process with more efficient, natural processes, free from solvents and other chemicals (the resulting APIs and finished dosage forms are marketed under the name PureActives®). The technology has enabled Centrient to reduce its carbon footprint by up to 65% relative to traditional chemical-based processes. More widely, removing fossil-based feedstocks from the company's broader manufacturing processes has led to a halving of the company's carbon emissions versus 2008 levels, putting Centrient on track to become carbon-neutral by 2030.

While Centrient and its peers are just one link in the wider pharmaceuticals value chain, the steps individual companies take to reduce the environmental impact of their manufacturing processes can have positive long-term outcomes for the industry and those who depend on it. By working together, expanding awareness and developing robust cross-sector stewardship, we can shape a more responsible, value-adding industry and safeguard the health and societal benefits of pharmaceuticals for generations to come.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Pharmaceuticals