

Pharma Pollution: An ignored cause of Antimicrobial Resistance

Event Minutes

On 10 December 2015, **EPHA** and **Health Care Without Harm Europe** organised an event in the European Parliament that discussed the links between AMR and environmental pollution, in particular focusing on antibiotics manufacturing and excessive use in livestock farming. The main consensus of the event was that all stakeholders - in particular industry and regulators - must push for enforceable standards and regulation to tackle the spread of AMR via the physical environment.

Opening

Event co-host and organic farmer **MEP Martin Häusling (Greens, Germany)** explained that the problem of overconsumption in animal husbandry is close to his heart. Far more antibiotics are given to animals than to people and too often their uses are non-therapeutic and unnecessary, triggering the development of resistant bacteria in livestock. Vaccination is not enough as a preventive measure. He deplored that, despite WHO warnings about a 'post-antibiotic era', 25,000 deaths annually in the European Union (EU) and an economic burden of 1.5 billion EUR, the European Commission's response to the fact that antibiotics are no longer working has been to focus on creating more antibiotics rather than addressing the causes and exploring viable alternatives. Solving a problem with the problem is not going to work.

Context

Moderator **Anja Leetz (Health Care Without Harm Europe)** welcomed the participants and presented the objectives of the meeting, which were to ensure that the often neglected environmental dimension of the One Health approach to tackling AMR are fully integrated into EU level debates, and to raise awareness of relevant issues pertaining to the manufacturing process of antibiotics and their use in agriculture and animal husbandry. She stated that transparency and reliable data are crucial to ensure that antibiotics will be effective in the future, and to have a clearer picture of who is prescribing and using them and the reasons thereof. She added that the organisers are keen to work with all parties in order to find sustainable solutions. The need to address AMR and pharmaceuticals in the environment is urgent and the event is part of a larger effort to build up understanding of the issue.

She then introduced **Sascha Marschang (European Public Health Alliance)** who explained that the event was the first fruit of EPHA's new campaign on AMR, which would be further developed in 2016 with a focus on a One Health approach. He described some of the public health consequences related to the diminishing effectiveness of antibiotics as a result of resistance and argued that the role of pollution as a contributor to the spread of AMR has so far



been little discussed at EU level. Water bodies, soil and sediment become contaminated during the manufacturing process and as humans and animals come into contact with the environment, resistant bacteria can easily cross the globe via international travel and trade. He also stated that it is important to discuss industry's role in this process, especially since companies are outsourcing much of their production of active pharmaceutical ingredients and finished dose products to emerging markets overseas, facilitated by lack of legislation. Global supply chains remain un-transparent.

However, he added that there was a glimmer of hope since the AMR threat had stimulated lots of activity at national, European and international level and in this context it was vital to ensure that responses were coherent and mutually reinforcing, including, *inter alia*, policies related to pharmacovigilance of medical products, water, and chemical policies. He concluded by stating that only a holistic and comprehensive approach that paid attention to human and animal health and the role of the environment, with public health values and priorities at the core, and all stakeholders assuming their responsibilities, could tackle this global health threat.

In a video address **Jim O'Neill, Chairman of the independent UK Review on AMR**, provided a brief outline of the Review team's work, which began in late 2014 in response to the realisation that AMR is the world's biggest health threat; at the time this was still little recognised outside of the scientific community. He stated that his team were charged with translating the scientific threat into an economic challenge. Their final report with very specific recommendations would be released in mid-2016 and used as the basis for an attempt to persuade the United Nations to draft an agreement to be signed by all countries by the autumn.

There are clear issues on the demand and the supply sides, which are covered by specialist reports on key issues. For example, the potentially crucial role for state-of-the art diagnostics to enable health professionals and other relevant stakeholders to dramatically reduce the use of antibiotics. The latest report, 'AMR in Agriculture and the Environment' calls for global limits of antibiotics use in agriculture. They've also produced a report on what's needed to get new and more useful drugs on the market. Moreover, they've addressed the need for more research on AMR and made a call for a global innovation fund academics could benefit from. They also persuade global policymakers and pharmaceutical industry stakeholders to get in line with their recommendations, and O'Neill congratulated the efforts by the EU, the WHO and FAO, and in particular the statement by the G7 Ministers, which called for action to implement many of the proposals made by the AMR Review. The AMR Review could translate this into G20 policy commitments under the Chinese leadership in order for the AMR problem to be tackled.

Natasha Hurley of Changing Markets, co-authors of the '**Bad Medicines**' report published by **SumOfUs**, explained that Changing Markets worked to achieve transformative economic change. Their research on global supply chains had revealed a complex web of links between some of the biggest Western pharma companies (including also generics drugs companies), antibiotic-producing factories in China and Indian middlemen. She deplored that plants in these countries were able to pollute in impunity, with obvious consequences for local communities and the environment given the levels of toxicity. In China this had led to a number of pollution scandals. There was a strong case for greater transparency of supply chains backed up by regulation, since companies needed to know what is and what isn't acceptable, and to create a



level playing field. Most challenges to sustainability were the result of market inertia. The threats emanating from AMR are so serious that there is no justification to deflect action.

Representing the **World Health Organization**, **Dr Roberto Bertolini** presented the new **WHO Global Action Plan** and underlined the need for alignment with the EU level in the battle against AMR. He presented the epidemiology of AMR but stressed that AMR is not a 'medical', but a social and economic issue which called for inter-sectoral coordination, international standards and data sharing. The development of AMR involves many different actors including the health sector (health systems, doctors, pharmacists, etc.), communities (patients, families), the agriculture sector, the private sector (e.g. pharmaceutical companies) and governments (e.g. regulatory authorities, politicians). He explained that the WHO has stepped up its efforts on AMR over the last 15 years and presented their work in the European Region on the food chain and surveillance (including global reports and networks covering Europe and Central Asia), stating that although antibiotic resistance was rising at a similar rate in EU and non-EU countries, there were big differences between countries when it comes to antibiotic consumption. He said that there was both a WHO European strategic action plan covering the Euro Region (2011-2020) and the Global Action Plan, which is supported by relevant guiding principles (e.g. whole-of-society engagement, sustainability, incremental targets) and contains five strategic objectives:

- Improve awareness and understanding
- Strengthen knowledge and evidence base
- Reduce incidence of infection
- Optimize use of antimicrobial agents
- Develop economic case for sustainable investment

He added that the Global Action Plan stipulates that all Member States are supposed to have in place national action plans two years following the endorsement of the draft plan, e.g. by 2017. He also informed that the first World Antibiotic Awareness Week had taken place in November 2015, aligned with the annual European Antibiotic Awareness Day, and went over the campaign messages related to the theme 'Antibiotics: Handle with Care'.

From the **European Commission**, **Helen Clayton, Directorate-General for the Environment**, talked about the **Water Framework Directive (WFD)** and stated that the Commission was trying to take a holistic approach to chemicals in the environment. DG Environment was collaborating with DG SANTE on pharmaceuticals in the environment, including on the issue of AMR. Progress on the Commission's Action Plan on AMR was currently under evaluation. DG SANTE is in the lead, but DG ENV will be involved in considering whether there are additional needs.

Under the WFD, a first watch list of substances was established in March 2015 to obtain monitoring data on substances of possible concern from the Member States. Some of them - two hormones and a painkiller – had been proposed for inclusion in the priority substances list but not been included in the 2013 revision of that list. Three antibiotics were also included in the watch list. However, more work will need to be done on how environmental concentrations might be linked with the threat of antimicrobial resistance. It will be important to not only look at antibiotics but also at levels of resistance to them.



A roadmap supporting the development of a strategic approach to pharmaceuticals in the environment would soon be released; a new study would be starting to complement the study commissioned by DG SANCO a few years ago to assess the scale of the problem and identify possible options to address it. The new study would be accompanied by a public consultation. On the basis of this the Commission will decide on the options to include in the strategic approach, followed two years later by a set of measures as appropriate, subject to impact assessment.

Susan Haffmans (Pesticide Action Network, Germany) addressed the rising problem of pharmaceuticals in the environment, stating that antibiotics contain biologically highly active substances. There is still poor knowledge of their environmental impact, especially since older products have never been subject to environmental risk assessments and post-authorisation monitoring is non-existent. Moreover, as yet there are no binding limits for pharmaceuticals in groundwater and surface water.

Ms Haffmans confirmed that antibiotics use in livestock production remains particularly high due to prophylactic and metaphylactic deployment; more antibiotics are given to healthy animals than to sick people. But antibiotic resistance also affects soil bacteria after the application of manure from treated animals, which is disturbing soil ecosystems. In addition, antibiotics and their metabolites also contaminate water bodies as they reach groundwater resources and have an impact on plants, algae and fish.

Policy options advocated by PAN Germany relate to both the market authorisation – risk assessment process and risk management and evaluation during the use phase. Legislation should be improved to better protect the environment and combat AMR. For example, the draft Regulation on veterinary medicinal products could be improved by including a regular renewal of all authorised veterinary pharmaceuticals (with an environmental review scheme), making available information from environmental risk assessments in a publicly accessible veterinary medical database, and introducing systematic environmental monitoring. A minimisation strategy for antimicrobials should be coupled with a general exclusion from authorisation for antimicrobials used as reserve antibiotics for humans, and for veterinary active substances which are highly hazardous to the environment.

Panel debate

The panel was moderated by **Dr Åke Wennmalm (Sustain Pharma)** who opened the session by introducing and analysing the different stakeholders and their respective roles in the process – policymakers and regulators, pharmaceutical producers and consumers of pharmaceuticals (including also hospitals and individuals purchasing antibiotics over-the-counter) – as well as their different targets and tools at their disposal. He also cited voluntary agreements, consumer power and lobbying for legal control (e.g. via Good Manufacturing Practices) as possible tools for action to counteract emissions of antibiotics from manufacturing plants.

The panellists were then asked to reflect on a cluster of questions, *inter alia* related to taking responsibility for better environmental management and green production methods, transparency of global supply chains, reducing excessive use, antibiotic stewardship and



changing the innovation model for antibiotics. He also stated that in order to make informed decisions, consumers needed to be well-informed about environmental issues.

Elizabeth Kuiper representing the **European Federation of Pharmaceutical Industries and Associations (EFPIA)** reported on several industry initiatives to support sustainable supply chains and environmental management, including the **Eco-Pharmaco-Stewardship (EPS) framework**. This framework looks at possibilities to manage environmental aspect in the whole lifecycle of pharmaceuticals from their research and development (R&D) phase, through usage phase till their disposal. Industry stands ready to contribute in all steps, but it is important to realise that true success requires collaboration between all stakeholders. She argued that it was equally important to adopt a life cycle approach, for local governments to introduce and enforce environmental legislation where it doesn't exist already, and implement sustainable procurement practices.

On transparency, **Adrian Van Den Hoven (European Generics Medicines Association)** affirmed that supply chains were already highly regulated and that any change in manufacturing is subject to a regulatory approval. Regulators are fully aware of the supply chain manufacturers and the idea that supply chains are un-transparent is untrue. There are a limited number of European GMP inspectors for quality inspections; adding additional environmental requirements as proposed by EPHA would stretch already over-stretched European inspectorates. He stated that another important contribution was industry auditing which includes environmental auditing.

Regarding manufacturing standards, he stated that there are different manufacturing techniques for different products. Industry tried to establish best practices, with many generics companies participating. These practices needed to be shared in order to move forward. He stated that the entire health community had to act to fight AMR, including e.g. doctors and pharmacists who have a role to play in advising patients on appropriate use of antibiotics. Improvements could also be made to prevent deaths in hospitals (where AMR is often transmitted due to ineffective infection control). The industry believed in rational prescribing of antibiotic medicines. It was also important to better understand the link between water pollution by antibiotics and the prevalence of AMR in humans.

Regarding the prioritisation of public health over profits, Van den Hoven stated that reimbursement prices were very low for various antibiotic products, e.g. in the UK, hence profits were not really made. The market for generics in Europe was bad since they are taxed to pay for speciality drugs. There was no economic incentive to produce older antibiotic medicines which are hardly used but which may be necessary to deal with a future threat of infection.

He stressed that industry was improving manufacturing processes and that there was an increasing number of initiatives to reduce antibiotic waste and take a life cycle approach, e.g. take-back-to-pharmacy schemes for expired medicines.

He doubted that patients would base their purchase decisions on environmental criteria since they mainly followed the advice of their doctors; moreover, in many countries patients did not have much of a choice where there are generic reference price (substitution) systems.



Kia Salin of the **Swedish Medical Agency** argued that authorities would do well to apply a 'carrot and stick' approach. She argued that environmental considerations should feature in public procurement processes and in the reimbursement system. Prescribers should only cover their costs. She also stated that forerunners should be encouraged, e.g. through environmental labelling, and stressed that legal tools are very important to raise pharmaceutical performance as a whole.

In Sweden, strict national regulation has achieved good results. She stated that preventive use of antibiotics in animals should be banned.

German holistic veterinarian **Dr Andreas Striezel** stated that the reduction in antibiotics in organic farming has also had an effect on resistance. From an environmental perspective, it is however crucial to discuss animal densities as there is a strong link between high stocking densities and pollution by high pharmaceutical deployment.

He stated that diseases among animals should not be increasing. Pigs have been more prone to pulmonary diseases since the introduction of the benchmarking system. The latter needed to be improved across the EU to cover animal health and welfare. Moreover, any prohibitions, e.g. regarding preventive use of antibiotics, needed to apply to all animals. The free sale of antibiotics for animals should be illegal.

Dr Striezel added that there was not much transparency between farmers and pharma industry, and Internet sales further hindered transparency.

The solution was not only to think of restrictions, but to find ways of promoting the right behaviours through education and appropriate policies. There should also be more competition to look at the best ways to keep animals.

Audience discussion

In the ensuing audience discussion, participants stated that it was difficult to rely on local and regional authorities to enforce regulations when it comes to the production of antibiotics. That is why companies have a special responsibility to apply pressure and engage with global suppliers around clean production standards.

Andreas Biesantz (EuroCAM) suggested that the Commission should consider alternatives to antibiotics, such as complementary and alternative medicines. Rather than focusing only on vaccination as a prevention measure, there should be an additional action point in the Commission's Action Plan on AMR that would cover alternatives to antibiotics.

Another CAM representative from the UK stated that there was lots of work in the world around alternatives to antibiotics. Too much emphasis was placed on the 'old' solutions. It has been eighty years since the first antibiotics were invented, it was now time to look at new solutions.

A representative of the **Society for Animal Medicines** agreed it was important to support the demand for alternatives to antibiotics, especially homeopathy. He also stated that it is important to define and monitor daily doses to know how much is actually given to animals for treatment, and for how long.



MEP Häusling stated that data availability is insufficient. Germany only recently discovered that so many antibiotics are being used, it is in fourth place in Europe per kg of meat. To this Ms Leetz added that EMA data is sales data, not usage data. It is thus also important to define what is being recorded.

Ms Kuiper stated that EFPIA welcomed alternatives to antibiotics. It was however also important to look more at diagnostics, all stakeholders needed to work on this together. Moreover, getting into conversation with authorities is crucial for their members.

She also stated that patient safety is key. Industry was determining the most important part, and how to act responsibly. EFPIA members would like to see a system where profits are not linked to the amount of antibiotics prescribed. GMP standards also implied controls and it is a regulated process which goes hand in hand with transparency - a 'licence to operate'.

A representative of **DSM Pharma** stated there are good examples in bulk chemistry. He explained that antimicrobial testing takes place at all their sites; they do this as a manufacturer. Legislation is required to create a level playing field across the full supply chain. Moreover, green purchasing initiatives should be introduced internationally.

A representative of **Astra Zeneca** informed that they have clear sustainability criteria covering safety, health and the environment. APIs are looked at through the Water Framework Directive perspective. They have audited 72 suppliers, and the information is available on their CSR pages, which are also externally audited – everything is very transparent. He added that procurers often do not recognise these pharma initiatives. Many responsibilities are industry focused, but other stakeholders needed to contribute too.

Ms Leetz stated that other companies had to follow the best practices that are being introduced. The same standards needed to be upheld across the entire industry.

Closing

In his closing speech, **MEP Jasenko Selimovic (ALDE, SWE)** referred to the negotiations over veterinary medicinal products which might help solve part of the problem.

He stated that his perspective differed from that of MEP Häusling in the sense that he has no problems with industry helping to solve the problem, also since new antibiotics are also needed. It was important that people from different perspectives worked on this together.

He stated that the number of deaths from AMR is horrific, and it's only the beginning. Global supply chains play a big role and they need to be addressed. He talked about ongoing work in the European Parliament including the negotiations over the veterinary medical products directive, which entailed In restricting routine preventive use, asking for a database on use, more pharmacovigilance, and a feasibility study on a monograph system for environmental risk assessment. All this will solve part of the problem.

However, he stated that the obvious lack of interest from the regulators' side will prevent success. There is lack of interest in three major players: 1) the Member States, and in particular those where antibiotics are routinely prescribed to people when they get sick because it is



profitable. In some countries, bad animal husbandry measures are also masked by using antibiotics. Governments are not acting in any way. 2) the European Commission, which has worked on this for a long time but is frequently postponing things, e.g. the animal health law will not deal with AMR but only the next one. The Commission knows that the Council will block it if they propose it. 3), the Council itself— in 2012 it said that all Member States should do their action plans, however 4 states still have not done this. Moreover, there are implementation gaps. More should be done, and more quickly.