JOINING THE DOTS.

Tackling Pharmaceuticals in the environment and AMR in Europe

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epha european public health alliance

Changing Markets FOUNDATION

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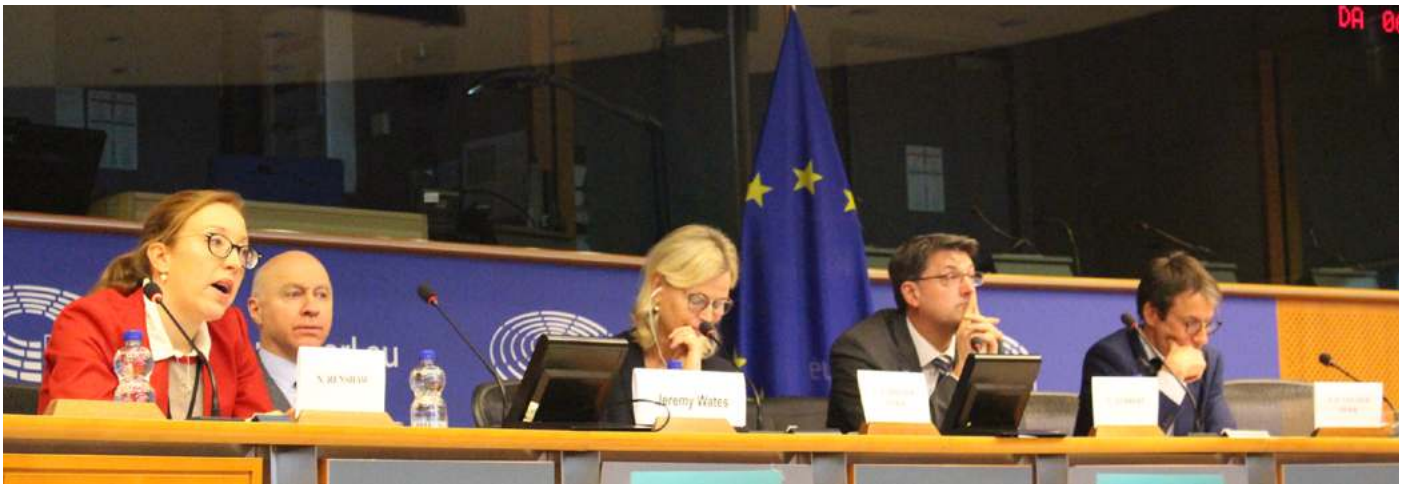


JOINING THE DOTS. TACKLING PHARMACEUTICALS IN THE ENVIRONMENT AND AMR IN EUROPE

The evolving policy debates about Pharmaceuticals in the Environment (PIE) and Antimicrobial Resistance (AMR) are closely interconnected and should not take place in separate silos. This event aimed to "join the dots" between the two by discussing environmental pollution caused by pharmaceutical consumption in Europe (where water bodies and entire ecosystems are under strain) and by the production process of antibiotics in third countries.

The upcoming EU strategy on Pharmaceuticals in the Environment and the implementation of the new EU One Health Action Plan against AMR provided the backdrop for a lively discussion featuring policymakers, international experts, civil society and industry representatives to highlight the different facets of – and available solutions to – tackling both issues.

Opening

Event host **Annie Schreijer-Pierik MEP** (EPP, Netherlands) highlighted upcoming evaluations of European water legislation and that regulations on levels of pharmaceuticals in the environment should be included in the legislation. She stated that although this threat was not monitored, increasing levels of pharmaceuticals were being detected in water not only from increased use but also increased need, e.g. due to Europe's ageing population. She underlined the importance of stakeholders - governments, producers, the medical community, civil society, etc. -working together.

Setting the Scene

EPHA Secretary General Nina Renshaw described the twin challenges of PiE and antimicrobial resistance, pointing out the increased need for policy coherence to ensure that public health and human health come first. She stated that action on PiE, (caused by, for example over-consumption of antibiotics,

irresponsible disposal of pharmaceuticals, run-offs from intensive farming, and inadequate sewage / wastewater treatment) was long overdue. Pharmaceuticals are polluting surface and ground waters, including major rivers like the Rhine and the Meuse, with negative impacts on water quality, drinking water supply, aquatic life, local ecosystems, and facilitating the spread of drug-resistant bacteria.

Ms Renshaw noted that the EUOne Health Action Plan against AMR, released in 2017, is weak in resources. Yet the threat is growing – in some cases, last-resort antibiotics are no longer effective – and AMR has the potential to be a bigger killer than cancer If no adequate and timely policy response is found. This could be a huge burden as routine medical procedures will become dangerous and no longer cost-effective. She argued that, **if AMR was one single disease, the European Commission would have pulled out all the stops; however, action is slow because AMR is complex and difficult to get a handle on.**

EPHA has made it clear that the EU should be doing more and not less. The new Action Plan should have made major progress on environmental pollution but has passed the buck. There is an upstream problem which means that while the quality of pharmaceutical products can be controlled through the Good Manufacturing Practices framework, this does not extend to environmental standards. EU countries acting together have the purchasing power to be part of the solution.
Renshaw acknowledged the voluntary initiatives coming from industry, but these were not getting to root of the problem given the opaque global supply chains, involving many different operators. EU measures must support progress in manufacturing countries like India and China. In closing, she expressed EPHA's hope that 2018 will be a turning point and that the ongoing public consultation on PiE, the Own Initiative report by MEP Kadenbach, and the upcoming review of the Water Framework Directive would lay the ground for improved measures to tackle AMR. Crucially, better data and measurable targets are required to drive things forward. In support of a multi-stakeholder, One Health approach, EPHA took the lead on a Joint Statement / Call to Action on AMR, endorsed by the members of the European Commission's Health Policy Platform.

Evidence

Prof Dr. Christoph Lübbert, Leipzig University Hospital (Germany) talked about the global rise in multi-resistant bacteria and implications for patients, explaining that AMR presents an age-old problem, amplified today by increased selection pressure, globalisation, poor governance and corruption in many health systems. The main drivers of AMR include excessive and inappropriate use of antibiotics in people and animals combined with environmental contamination from manufacturing discharges.

Resistance genes spread rapidly from the environment to the community and healthcare settings. The increase in global drug production,

mobility (e.g. high rates of multi-drug resistance have been detected in patients returning to Europe from abroad), medical procedures (e.g. commercial kidney transplants, cosmetic surgery) and intensive agriculture / livestock production are fuelling AMR. Pharmaceutical residues from production plants become a reservoir for the development of AMR, something that is particularly problematic in India where more than 80% of generic drugs are produced. While the life-saving work of the UN agencies would not be possible without the bulk production of affordable medicines and vaccines, price pressure is increasingly being exerted at the expense of the environment.

To investigate the extent of environmental pollution in more detail, Prof Lübbert and a team from the North German Broadcasting Corporation (NDR) travelled to Hyderabad and produced a documentary. They found that a good number of pharmaceutical companies in India clearly do not meet European standards; for example, many factories are not connected to functioning sewage networks. High levels of antibiotics and antifungal agents were found in effluent discharges, including fluoroquinolones, fluconazole and voriconazole, which are vital for the treatment of severe infections. When flooding hit the area in 2017, highly toxic wastewater poured into rivers which poisoned aquatic wildlife in an unprecedented scale. Moreover, the mortality rate of neonates in the Delhi area due to MDRO (multidrug resistant organisms) infections reached 50-60%, compared to less than 10% in Western Europe.

KPC (Klebsiella pneumoniae Carbapenemase) producing Enterobacteria present a good example of the global spread of “superbugs” – from the USA to South America, Asia, Israel, and then to Greece, where the health system is already under strain due to the economic crisis. European hospitals have to pay close attention to screening patients: the transfer of a patient from Greece led to a significant KPC outbreak in Leipzig that caused multiple deaths, mostly affecting already immune-suppressed patients.

Remaining in Europe, Prof Dr Jan Peter van der Hoek, EurEau and TU Delft (Netherlands) further discussed the growing problem of pharmaceuticals in the water cycle, stating that the latter is composed of man-made water transport infrastructure and the natural water system including wastewater treatment effluents, surface waters, groundwater and drinking water. Crucially, water bodies are not restricted to natural borders. They are threatened by, inter alia, pesticides, nanochemicals, endocrine disruptors and pharmaceutical drugs, the latter due to production sites, healthcare uses and consumption of prescription drugs, agriculture, etc. Increasingly, new combinations of PiE are found that were not present in the past or that could not be detected.

Samples taken across Europe show a deteriorating quality of water in rivers (only about 10% from over 100 European rivers in 27 European countries were clean), groundwater (411 emerging contaminants were detected at 494 groundwater sites in France). In 2013, the Netherlands screened drinking water sources

for pharmaceutical residues; 99 were detected more than once, with a long list of substances found in the Rhine and Meuse rivers. The increased presence of PiE compromises drinking water quality and the principle that access to safe water and to medicines is a human right.

Noting that a great number of abatement options exist, including source protection - the precautionary principle applying both to the Water Framework Directive (article 7) and the Drinking Water Directive - Prof van der Hoek argued that end of pipe solutions are not sustainable, both in terms of cost and effectiveness. However, a number of less costly solutions should be explored further; these include take-back schemes, green pharmaceuticals, eco-labels on packaging, compulsory prescription of pharmaceuticals with high environmental impact, awareness-raising and promotion of healthy lifestyles. Crucially, their success relies on active collaboration between all stakeholders at different levels.

In this regard, the Dutch chain approach could offer a way out as it looks at the entire life cycle of PiE and involves close cooperation between central government, regional water authorities and hospitals.

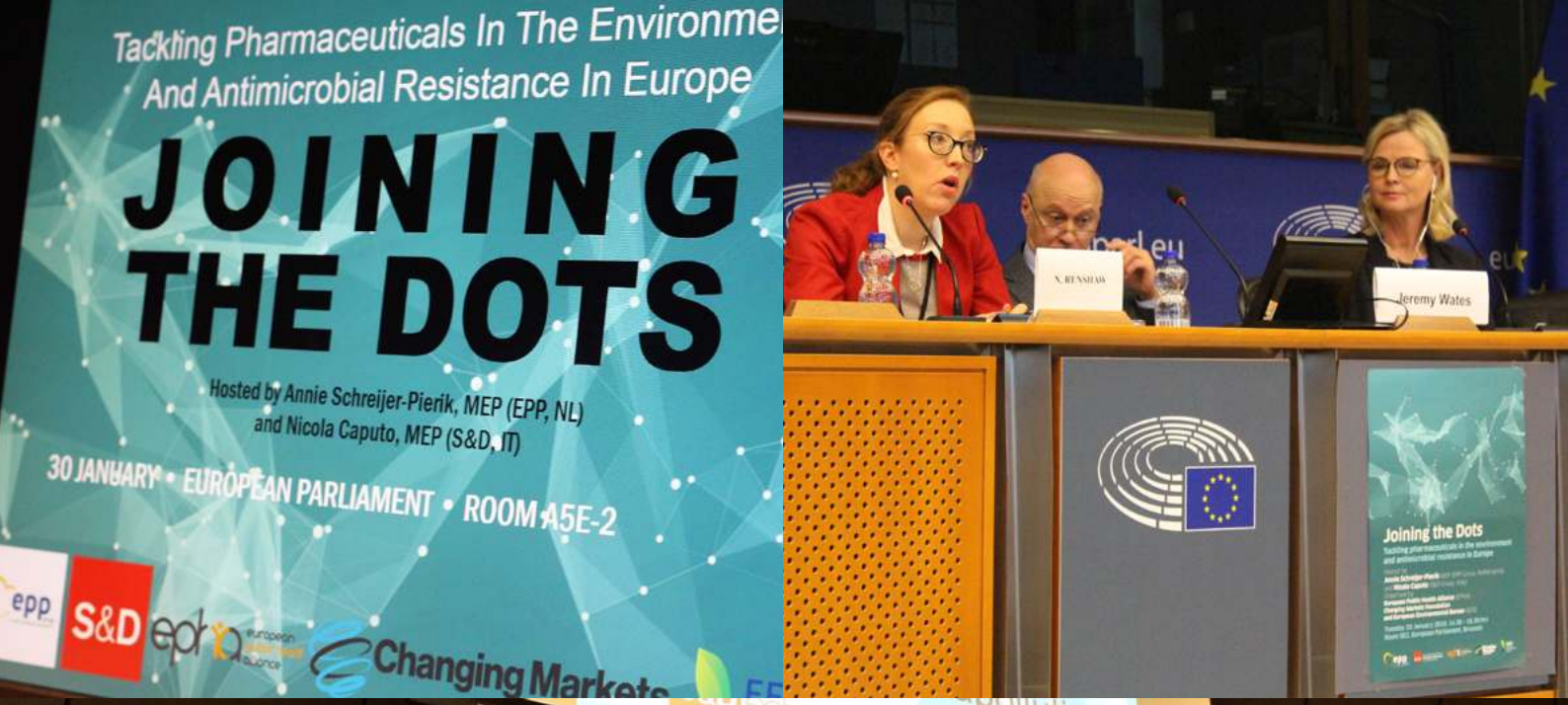
During the discussion, commentators noted that the existing evidence of PiE presents a huge risk, which required a more effective regulatory response at the European level. It was also important to determine who should bear the financial responsibility. While EPHA evoked the “polluter pays” principle enshrined in the treaties, Prof Lübbert argued in favour of extended producer responsibility, whereby environmental costs are already integrated into the market price charged to users. In Hyderabad, companies were often trying to cut corners even where water treatment exists, activities that are neither monitored nor controlled.

Ms Schreijer-Pierik highlighted that the issue has been discussed at length in the European Parliament, where a lot of amendments were approved. However, not all countries were taking a strong approach, hence there is a need to review everything to determine effective implementation.

Panel discussion: Policy And Practical Solutions - How Can Europe Tackle The Problem?

Moderator **Jeremy Wates, Secretary General** of the European Environmental Bureau (EEB) expressed his hope that the European Commission’s strategic approach to PiE would include robust and effective measures. He recalled past discussions about REACH (the EU regulation for the registration, evaluation, authorisation and restriction of chemicals): policy measures were first opposed by industry, then they were welcomed. The costs of inaction on PiE and AMR are too significant to delay action any further.

Kicking off the panel, **Dr Caroline Moermond** (RIVM, Netherlands) talked about the


Tackling Pharmaceuticals In The Environme
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Hosted by Annie Schreijer-Pierik, MEP (EPP, NL)
and Nicola Caputo, MEP (S&D, IT)
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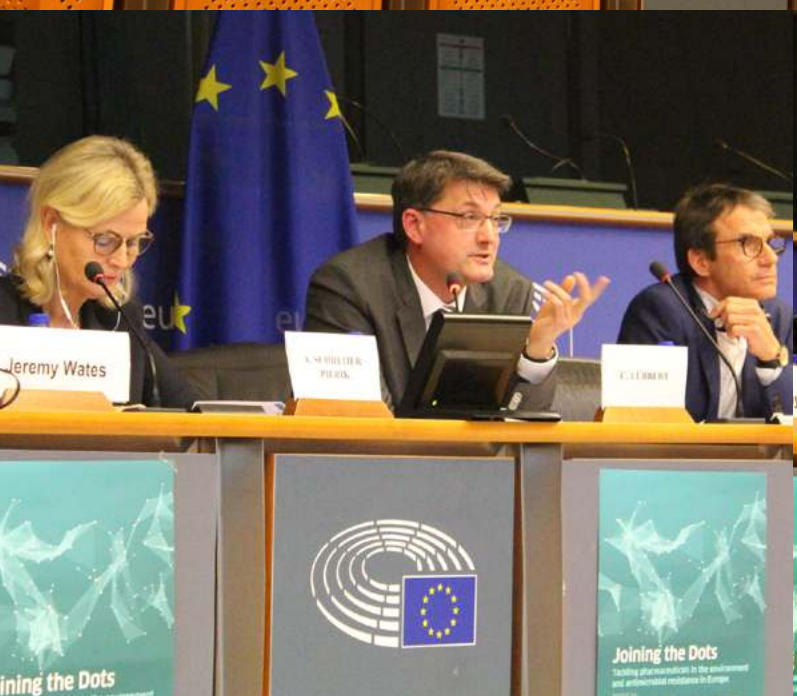
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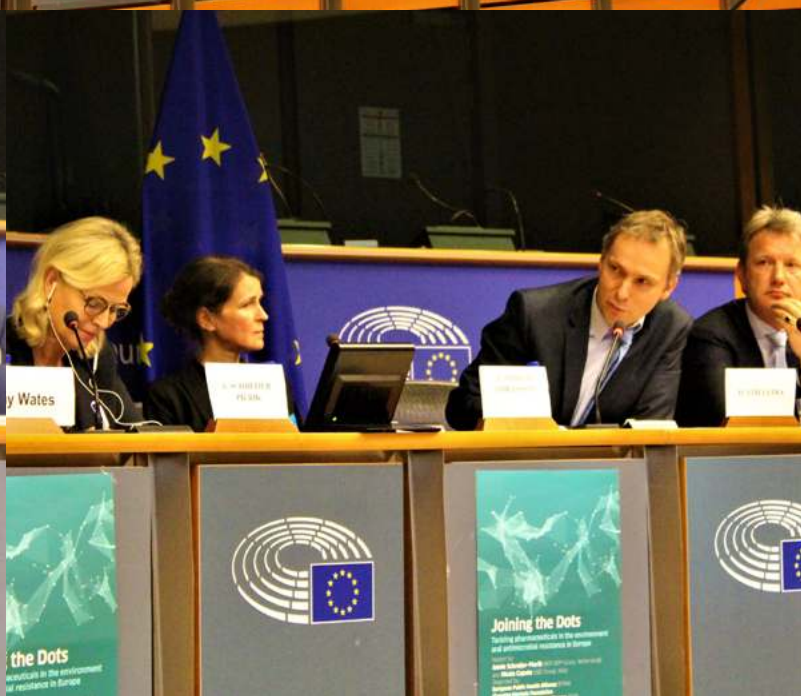
Joining the Dots

process for carrying out environmental risk assessments (ERA) of human pharmaceuticals . She explained that ERA is used to compare the predicted environmental concentration (use) to the predicted no effect concentration (possible risk).

Importantly, Dr Moermond highlighted that ERA only assesses exposure through use and does not take into account the production of drugs. Moreover, it is product-based, meaning that different products containing the same active ingredient result in different files that might generate different conclusions since different tests are performed. No ERAs are undertaken for old products, and they do not make reference to other environmental legislation (e.g., Water Framework Directive) nor do they assess the risk of AMR. **She also underlined that, in human medicine, ERA is not part of the benefit/risk analysis, i.e. the results cannot be grounds for refusing marketing authorisation. This differs from veterinary pharmaceuticals used in food-producing animals, where identified risks could lead to restriction of use.** The question is how best to weigh environmental factors against health and economic benefits.

Most ERAs are performed according to guidelines, but nonetheless the debate about what information applicants should provide to demonstrate that a product is safe remains open, while competent authorities differ in their approach. Dr Moermond proposed reorganising ERA to a substance-based framework and better embedding of ERA expertise at European level. This would include a framework to assess and weigh risk management options, the monitoring of all pharmaceuticals with environmental risk, updating ERAs for older products, and designing specific measures for pharmaceuticals with environmental risk. She also argued for better information for healthcare professionals regarding substitution of risky drugs and improved research on wastewater techniques to tackle PiE and AMR simultaneously.

Following on from where his colleague left off, **Marc de Rooy, Dutch Ministry for Infrastructure and Water**, reported on experiences with the Dutch chain approach, informing the audience that it was set up in 2016 to reduce pharmaceutical residues in water. The programme promotes multi-stakeholder dialogue to tackle the entire pharmaceuticals chain, with measures identified for each step: development and authorisation, prescription and use, waste and sewage treatment.

Critically, de Rooy stated that actions must be taken in parallel. **In the Netherlands, this was working well, not least because the water and healthcare stakeholders were meeting and collaborating. The Dutch approach is pragmatic and takes into account access to medicines concerns.** But since the problem does not stop at national borders, similar approaches should be adopted in other member states.

Talking about public procurement as a tool to reduce PiE and AMR, **Lena Göransson Modigh, representing the Västra Götalandsregionen** (Western Sweden) **described how central purchasing (procurement) decisions at regional level can make an important impact.**

She explained that her department served the needs of 54,000 employees – mostly nurses and doctors – and that it drew up a list of criteria that is being used in central purchasing. Moreover, the team carries out desktop audits, performs checks in pharma plants, and works together with the Swedish national agency for procurement to develop new criteria related to PiE.

An industry perspective on PiE and AMR was provided by **Lucas Wiarda**, representing leading manufacturer of sustainable pharmaceuticals, **DSM-Sinochem**. Mr Wiarda agreed with the need for a multi-stakeholder approach to address complex matters, among them access issues, irresponsible use, developing new antibiotics, but also responsible manufacturing. Many industry players were increasingly concerned about PiE and AMR, and it was not the pharmaceutical industry's intention to pollute the environment, or contribute to the spread of AMR. He also pointed out that antibiotics enter the environment in different ways, i.e. also following human consumption and irresponsible use in the animal health sector.

A number of companies have already developed measures. The Davos Declaration, the commitments presented by the industry at the UN General Assembly meeting in September 2016 and the recent progress report by the AMR Industry Alliance were examples that supply chains and practices are under review, and that a common manufacturing framework is being developed. The AMR Industry Alliance Report refers to many initiatives that demonstrate companies' engagement to define safe emission levels as it was also in the industry's interest to curb AMR. However, other stakeholders also need to act.

Wiarda cautioned that the Alliance only represents about 40% of global manufacturing capacity; the remaining majority needed to follow suite and implement the same standards. While some stakeholders were sceptical of self-regulation, he described it as the fastest route to bring about change, with minimum requirements by the Alliance already in place. However, some companies are willing to go further if a level playing field is created – they are not against regulation as such. The introduction of regulations depended on political will, and it was also quite time-consuming as it required enforcement authorities, audits, etc. Clearly, transparency must be improved, and regulators were needed for this. Ultimately, it would be key to involve insurance companies, buyers, governments and pharmacies in this debate. The existing tender systems in Europe make medicines too cheap, especially generic antibiotics. Therefore, decisions were commonly made on price only, which incentivises low standards.

The final speaker, **Hans Stielstra (Deputy Head of the Clean Water Unit, DG Environment)** contributed the European Commission response to the issues addressed during the discussion. He made it clear that the long overdue PiE strategy, now due to be released by May 2018, is not only about water but holistic

in scope. While it will not propose any legislative changes, it could indicate relative legislative instruments to be explored in the future, as well as undertaking a needs impact assessment. He confirmed that it would contribute to the Commission's approach to AMR and present a broad range of feasible policy options along the pharmaceutical chain. Two stakeholder consultations had been launched by the Commission, one for the general public, the other aimed at an expert audience.

Stielstra added that manufacturing of pharmaceuticals in China and India was one of the more problematic issues, and policy options to acknowledge the international dimension should be included in the PiE strategy. The upcoming review of the Water Framework and Urban Wastewater Treatment Directives also needed to be tweaked to address issues related to PiE. He welcomed industry's openness to exploring potential legislative options. The Dutch chain approach, was an attractive programme, but the question remained if it could also be applied at EU level or in other member states.

Importantly, the public consultation aimed to determine where the European PiE strategy could add value in addition to what is happening already, e.g. regarding the improvement of standards. The Swedish approach to procurement was powerful, but it needed to be reinforced by trade policy, meaning that DG TRADE also needed to be involved in the discussions.

Discussion

During the discussion, a representative of Changing Markets, co-authors of a new study on pollution from pharmaceutical factories in India jointly published with the Scandinavian bank Nordea[1], explained that investors are increasingly viewing pollution in terms of the business risk it presents. The new report updates their 2016 report, which highlights the occurrence of high levels of toxic solvents and heavy metals in water near production sites in India and China. These factories were all exporting pharmaceuticals to Europe. European consumption was part and parcel of the problem, which is why Europe needed to act swiftly. This would set a positive precedent and cement Europe's role as a global lead region on the issue.

A representative of the European Federation of Pharamceutical Industries and Associations (EPFIA) acknowledged that industry was responding to many of the questions raised. The Eco-Pharmaco-Stewardship Framework developed during 2017is one example of action – this takes a holistic, lifecycle approach and contains actions to be taken at each step. While a number of regulatory tools already exist, certain tools could be further developed, e.g. extending ERA schemes to look at APIs during the whole lifecycle. Public-private partnerships like the Innovative Medicines Initiative and multi-stakeholder campaigns could serve to raise awareness, e.g. campaigns on medicines disposal.

The role played by nurses was highlighted by

1. Hyderabad's pharmaceutical pollution crisis: Heavy metal and solvent contamination at factories in a major Indian drug manufacturing hub

the European Specialist Nurses Organisation (ESNO). Misinformation was widespread and communication to patients often lacking.
A commentator from the European Federation of Water Services argued there would need to be a payment scheme in place for the proposed policy measures, but it was up to manufacturers to change. Extended producer responsibility could be one way, similar to toy manufacturers being responsible for over use of plastics.
Jeremy Wates stated that the "polluter pays" principle was not about punishing industry but to encourage responsible behaviours. Since industry practices influence pricing, government action is needed to set standards and develop policy measures that counteract the inactivity of laggards.

Panellists remarked that the culture of dialogue that exists in the Netherlands isn't commonplace across Europe; the question is who has the power to prevent stakeholders from discharging pharmaceuticals into the environment.
Dr Moermond noted that industry proposals were not always welcomed by regulators. The majority of industry proposals are good, but it should not be a voluntary effort.

Prof Lübbert expressed his concern that German health insurers were only looking at prices to base their purchasing decisions on.
Mrs Göransson Modigh pointed out that, despite ongoing dialogue with other Nordic countries about green procurement, their combined market share remained very small (about 2% of global medicines) and therefore a combination of actions should be taken. For example, the Swedish MPA has a government mandate to work at the EU-level to lobby for the implementation of environmental criteria implemented in Good Manufacturing Practice regulations.

Prof van der Hoek explained that, in Switzerland, citizens are levied 9 francs per person to pay for the cost of upgrading water treatment facilities ; this could also be explored by the Commission.
Mr Wiarda recalled that lack of access to antibiotics is still causing more deaths than AMR, and that the number of supply issues is increasing because of price pressure. He said the assumption that prices would rise if the playing field between generics and originator producers was levelled was a myth.

In closing, MEP Schreijer-Pierik reiterated that clean water and tackling the consequences of medical residues is a very important topic for European citizens- the reason for submitting a question to the Commission three months ago. The Commission was doing good work, but not everybody was on the same page. She called on the pharmaceutical industry to take things further as PiE bears serious consequences for drinking water and the spread of AMR. At European level, the right policy tools and instruments were needed so that action could be taken before the European Parliament elections in 2019.

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