European Commission releases strategy addressing pharmaceuticals in the environment

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The risks posed by pharmaceuticals in the environment have been mentioned increasingly over the past years as an emerging problem. Article 8c of Directive 2008/105/EC on environmental quality standards in the field of water policy mandated the European Commission to develop a strategic approach to water pollution by pharmaceutical substances. This long-awaited strategic document has now been released.

The 'Communication on a Strategic Approach to Pharmaceuticals in the Environment' outlines actions which aim at addressing the problems caused by pharmaceutical products entering the environment during their manufacture, use and disposal. The European Commission will approach this problem through the following:

- ▶ Increasing awareness and promoting the prudent use of pharmaceutical.
- ▶ Supporting the development of pharmaceuticals intrinsically less harmful for the environment and promoting greener manufacturing.
- ▶ Improving environmental risk assessment and its review.
- ▶ Reducing wastage and improving the management of waste.
- ▶ Expanding environmental monitoring.
- ▶ Filling knowledge gaps.

The actions included in the Communication will be initiated, continued or in some cases even be completed in 2020. The involvement of Member States as well as relevant stakeholders is envisioned to jointly tackle the problem of water pollution by pharmaceuticals and antimicrobial resistance.

FIRST MEETING OF EU'S COALITION FOR VACCINATION

On 4 March, the European Commission brought together Member State representatives and healthcare professional organisations on the topic of vaccination. The group discussed the need to form a European Union (EU) Coalition for

Vaccination comprised out of all relevant actors at the European level to combat vaccine hesitance and to better equip healthcare professionals with the skills needed to discuss this topic with their peers and patients.

The European Association of Hospital Pharmacists (EAHP) used this occasion to release the Association's Opinion on Vaccination, which welcomes the Council Recommendation on strengthened cooperation against vaccine-preventable diseases on the basis of which the EU Coalition for Vaccination was launched. In its opinion the EAHP recommends the vaccination of healthcare workers to keep themselves and their patients protected. In addition, the EAHP addresses the problem of vaccine hesitance, which should be countered through campaigns tackling online vaccine misinformation and developing evidence-based information tools and guidance to support Member States in responding to increased rates of vaccine hesitancy.

Also the problem of vaccine shortages is being addressed, in particular since the 2018 EAHP Medicines Shortages report showed that the shortage of preventable medicines rose from 20% in 2014 to 43% in 2018. The EAHP consequently calls on European institutions to carry out a Europe-level investigation into the causes of medicines shortages, including vaccine shortages.

AMR: JOINT BRIEFING NOTE OF ECDC AND OECD

To better address the growing problem of antimicrobial resistance (AMR), the European Centre for Disease Prevention and Control (ECDC) and the Organisation for Economic Co-operation and Development (OECD) have produced a briefing note on this topic for European Union (EU) and European Economic Area (EEA) countries. The document provides key estimates on the health and economic impact of AMR, as well as effective strategies that could help to diminish the increasing resistance levels.

AMR is a major concern for all EU Member States, but as highlighted in the briefing note this concern can be addressed at low cost by means of promoting better

hygiene in healthcare services, increasing the utilisation of stewardship programmes that are promoting more prudent use of antibiotics, decreasing the overprescription of antibiotics, and offering rapid testing for patients to determine whether they have bacterial or viral infections. Mass media campaigns should be used to make the general public more aware of the problem. A mixed intervention package, comprised out of these measures, could save about 27 000 lives per year across EU/EEA countries.

UPDATES FROM THE EUROPEAN MEDICINES AGENCY IN MARCH 2019

At the end of March, the European Medicines Agency (EMA) released information on the commencement of a review on screening patients before treatment with fluorouracil, capecitabine, tegafur and flucytosine. In addition, the agency advised on the increased risk of blood clots in the lungs and death with higher dose of Xeljanz (tofacitinib) for rheumatoid arthritis and confirmed that omega-3 fatty acid medicines are not effective in preventing further heart problems after a heart attack. In relation to Brexit, the EMA shares a question-and-answers document for patients and healthcare professionals outlining how different European institutions are working together to prevent medicines shortages.

Q&A: avoiding medicines shortages due to Brexit

The European Medicines Agency (EMA) has published a question-and-answers (Q&A) document for patients, healthcare professionals and the general public on the preparatory work that European Union (EU) authorities are doing to prevent medicine shortages due to the UK's withdrawal from the EU. It explains that in case of a withdrawal agreement, there will be a transition period during which EU law will continue to apply in the UK. This means that access to medicines will not be affected.

If the UK leaves without a withdrawal agreement or deal ('no-deal scenario'), EU law will cease to apply in the UK. In this case, in order to be able to continue to supply medicines in the EU, companies carrying out certain activities in the UK will need to make changes to comply with EU law.

The Q&As explain how the EMA, the European Commission and the EU/European Economic Area Member States have been working closely together since May 2017 to advise companies on how to apply for the necessary changes in order

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to minimise the impact on the supply of medicines, if the UK leaves the EU without a withdrawal agreement. The document underlines that Brexit will not impact the safety of medicines, nor the way they are evaluated. The EMA and the Member States will continue to monitor the safety and efficacy of medicines without any changes. This document applies to both human and veterinary medicines and will be updated as necessary.

Review on screening patients before treatment with fluorouracil, capecitabine, tegafur and flucytosine

The European Medicines Agency (EMA) has started a review of medicines containing fluorouracil (also known as 5-fluorouracil or 5-FU) and the related medicines capecitabine, tegafur and flucytosine, which are converted to fluorouracil in the body. The review will examine existing screening methods and their value in identifying patients at increased risk of severe side effects.

Fluorouracil (given by injection), capecitabine and tegafur are cancer medicines, whereas topical (applied to the skin) fluorouracil is used for various skin conditions and flucytosine is a medicine used in severe fungal infections.

It is known that some patients lack a working enzyme called dihydropyrimidine dehydrogenase (DPD), which is needed to break down fluorouracil. Prescribers may be unaware that their patients lack working DPD, and if these patients are given fluorouracil or related substances their bodies cannot break fluorouracil down, resulting in its build-up in the blood. Patients with a complete deficiency of DPD should therefore not be given fluorouracil, or medicines that can form it in the body.

The product information for most of these medicines states that they should not be used in patients with complete DPD deficiency. Genetic testing for DPD deficiency is recommended for most medicines used in the treatment of cancer, but systematic screening for DPD deficiency before starting treatment is not mandatory. In addition, new data on genetic testing and other DPD screening methods were recently published which may impact current recommendations.

The EMA will now assess the available data in relation to existing screening methods to detect DPD deficiency and recommend whether any changes are needed to the way these medicines are used in order to ensure their safe use.

EMA communication: increased risk of blood clots in the lungs and death with higher dose of Xeljanz (tofacitinib) for rheumatoid arthritis

The European Medicines Agency (EMA) is advising healthcare professionals and patients not to exceed the recommended dose of Xeljanz (tofacitinib) when treating rheumatoid arthritis. The advice follows early results from an ongoing study (study A3921133) in patients with rheumatoid arthritis which showed an increased risk of blood clots in the lungs and death when the normal dose of 5 mg twice daily was doubled.

In the European Union (EU), 5 mg twice daily is the authorised dose for rheumatoid arthritis and psoriatic arthritis. The higher dose of 10 mg twice daily is approved for the initial treatment of patients with ulcerative colitis.

The EMA is assessing the early results and will consider if any regulatory action is needed. In the meantime, patients with rheumatoid arthritis who are receiving Xeljanz at 10 mg twice daily in study A3921133 will have their dose reduced to 5 mg twice daily for the remaining duration of the study.

The aim of the study was to look at the risks of heart and circulatory problems with Xeljanz in patients 50 years of age or older who were already at higher risk of these, and to compare its safety with that of another medicine called a tumour necrosis factor inhibitor.

While full results are awaited, the EMA is recommending that healthcare professionals monitor patients for signs and symptoms of blood clots in the lungs. Patients should not stop or change their dose of Xeljanz without talking to their doctor. Patients should seek medical attention immediately if they experience symptoms such as difficulty breathing, pain in the chest or upper back, and coughing up blood.

Healthcare professionals are being informed in writing of the preliminary results of the study and the current treatment recommendations. There are other ongoing clinical trials in the EU with Xeljanz at a dose of 10 mg twice daily. Patients taking part in clinical trials with Xeljanz should speak to the doctor giving it to them if they have any questions or concerns.

Omega-3 fatty acid medicines

The European Medicines Agency (EMA) has confirmed that omega-3 fatty acid medicines containing a combination of an ethyl ester of eicosapentaenoic acid

and docosahexaenoic acid at a dose of 1 g per day are not effective in preventing further problems with the heart and blood vessels in patients who have had a heart attack. This is the outcome of a re-examination requested by some of the companies that market the medicines concerned, following the EMA's original recommendation in December 2018.

This means that these medicines should no longer be used in this way. However, they can still be used to reduce levels of certain types of blood fat called triglycerides. The EMA concluded that the marketing authorisations of these medicines should be updated to remove this use.

For more information please visit the EMA's website at <https://www.ema.europa.eu/>.

OECD REPORT ON THE USE OF ROUTINELY COLLECTED DATA

The Organisation for Economic Co-operation and Development (OECD) shared insights on the usefulness of routinely collect data on prescribed and dispensed medicines for health systems. The report analysed how patient-level data on medicines gathered from different administrative sources, such as pharmacy records, electronic health records and insurance claims, are exploited. It shows that such data are a key component for patient interaction with healthcare systems which should be used better.

Data were gathered from 26 OECD and European Union member countries which responded to a survey addressing the availability and accessibility of routinely collected data on medicines and their applicability to developing evidence. Medicines dispensed in hospitals are rarely covered by the sources that were reviewed for the report and consequently the hospital sector was identified as an information gap. Moreover, the report revealed that the widely collected routine data are not systematically used to inform pharmaceutical policies but rather to monitor consumption and national-level spending (22 countries), providers' compliance with guidelines (18 countries) or prescribing quality and behaviour (15 countries).

The report recommends the further development of methods to increase the leverage of routinely collected data as well as the improvement of cross-border knowledge sharing. In addition, it underlines the need to invest into data infrastructure and data governance.

AMR CONTINUES TO REMAIN HIGH

Data released at the end of February by the European Centre for Disease Prevention and Control (ECDC) and the European Food Safety Authority (EFSA) on antimicrobial resistance (AMR) in zoonotic and indicator bacteria from humans, animals and food indicate that AMR is showing no signs of slowing down. In particular, the analysis reveals that antimicrobials used to treat diseases that can be transmitted between animals and humans, such as campylobacteriosis and salmonellosis, are becoming less effective.

The information that was analysed jointly by the ECDC and the EFSA stems from data gathered via the 28 Member States of the European Union, Iceland, Norway and Switzerland throughout 2017. When comparing the newly released data with the summary reports from the past years, the rise in AMR becomes evident. The report focuses on data regarding *Salmonella* and *Campylobacter* isolates from humans and fattening pigs, as well as data on indicator *Escherichia coli* from fattening pigs and calves under 1 year of age and meat derived thereof. A few Member States also reported data on the occurrence of methicillin-resistant *Staphylococcus aureus* in animals and food.

Resistance to fluoroquinolones (such as ciprofloxacin) has become so high in *Campylobacter* bacteria in some countries that these antimicrobials no longer work for the treatment of severe campylobacteriosis cases. In *Campylobacter*, also high to extremely high proportions of bacteria were found to be resistant to ciprofloxacin and tetracyclines. However, combined resistance to critically important antimicrobials was very low to low in *Salmonella* and *Campylobacter* from humans and animals and in indicator *E. coli* from animals.

EMA BOOKLET ON THE JOURNEY OF A CENTRALLY AUTHORISED MEDICINE

The European Medicines Agency (EMA) has published a booklet describing the journey of a medicine for human use which is authorised by the agency via the centralised procedure. The booklet covers the journey of the authorisation from initial research to discussions on patient access to medicines across the European Union. It describes in particular how the EMA supports medicine development by providing scientific advice and how it assesses a medicine's benefits and risks once it receives an application for marketing authorisation. All the steps

involved in these processes, including the involvement of patients, healthcare professionals and other external experts, as well as the principles guiding the scientific discussions, are outlined.

READ UP ON EMA/HMA TALKS REGARDING HUMAN AND VETERINARY MEDICINES AVAILABILITY

The results of the European Medicines Agency's (EMA) stakeholder workshop on 9 November 2018 on the prevention and management of authorised medicines availability have been published. The event gathered representatives of patients, consumers, healthcare professionals, industry and regulators to discuss and contribute to the activities undertaken by the joint Head of Medicines Agencies (HMA)/EMA Task Force on the availability of medicines.

The key takeaways coming out of the meeting were the following:

- ▶ All stakeholders agree that medicines shortages are a problem of great concern.
- ▶ Close collaboration, transparency and public communication between all stakeholders are crucial since quick solutions are not available.
- ▶ The pharmaceutical industry plays a crucial role in preventing and managing the issue.
- ▶ Improved reporting requires a harmonised European Union (EU)-wide shortage definition, together with adequate metrics.
- ▶ Whether a minimum period for time out and information on pack sizes should be included in the shortages definition requires further discussion.
- ▶ Public communication should be constantly updated and refer to the expected duration of the shortage, any recommended or suitable alternatives, and other relevant clinical suggestions.

Among the more palpable results of the discussion, the EMA presented a draft best practice guide for public communication which points to a catalogue format as the ideal tool, as well as a draft EU regulator's manual on tools and guidance. Also, a proposal for a new EU-level shortages notification system or a single point of reference for better monitoring, prevention, management and communication was shared. Participants agreed that one of the greatest impediments in developing a united EU approach was the lack of a common definition of shortages.

The HMA/EMA Task Force was set up to develop and coordinate actions to guarantee uninterrupted supply of human and

veterinary medicines. This body comprises three thematic working groups focusing on marketing authorisations, supply chain disruptions and public communication on shortages.

EPHA RELEASES STUDY ON AMR NATIONAL ACTION PLANS IN EUROPE

The European Public Health Alliance (EPHA) published a study that analysed and mapped the implementation of National Action Plans (NAPs) or similar initiatives on antimicrobial resistance (AMR) in different European countries. The report covers 31 European countries, including the EU-28, Iceland, Norway and Switzerland, and highlights that good practice examples coexist alongside poor practices and inaction.

The implementation and development of NAPs are mixed with Southern and Eastern European countries generally trailing behind the rest of Europe. In addition, considerable variations have also been found in relation to the adoption of the European Commission's 'One Health approach'. Only 50% of the analysed countries have considered this approach when drafting their NAPs. Examples of NAPs in the report are presented in accordance with the following thematic areas:

- ▶ Encompassing a One Health approach.
- ▶ Including financing estimates and identification of funding sources.
- ▶ Integrating implementation and evaluation mechanisms.
- ▶ Identifying clear measurable goals.

The report concludes that most NAPs contain elements from the 2016 Council conclusions on AMR. This is underlined by the fact that 60% of NAPs and initiatives refer to infection prevention and control, as well as awareness-raising among professionals and the general public as one of their main priorities. Compliance rates with the WHO's Global Action Plan on AMR are considerably lower. Only a few countries mention information on financial resources or dedicated funds available for implementation, performance or monitoring indicators, as well as time-bound targets in both the human and veterinary sectors.

The study sets out a number of recommendations for policy-makers in the European Commission and within national governments, including the introduction of measurable targets, the allocation of adequate funding at the European Union and national level, and taking action to tackle pharmaceuticals in the environment. Civil society should be engaged in

the development and revision of action plans.

EHEALTH NEWS: EC RECOMMENDATION ON A EUROPEAN EXCHANGE FORMAT OF ELECTRONIC HEALTH RECORDS ADOPTED

On 6 February, the European Commission (EC) adopted the Recommendation on a European Exchange Format of Electronic Health Records, which refers to how electronic health records can be accessed and shared more easily between European Union (EU) Member States. The main benefits of using electronic health records are the following:

- ▶ Provision of effective and timely treatment by allowing healthcare professionals immediate access to the patient's health information (chronic conditions, allergies, intolerances to certain medications) while he/she is travelling inside the EU.
- ▶ Increase quality and ensure continuity of adequate care as citizens move around the EU.
- ▶ Safe data sharing that will support medical research.
- ▶ Increase health systems' efficiency and sustainability by allowing free and immediate medical data (laboratory or radiology tests) sharing between hospitals.

The European Association of Hospital Pharmacists contributed by giving feedback on the EC's Roadmap at the end of 2018 by pointing out the need to involve hospital pharmacists in the design of common standards, technical specifications of categories of health information, repositories and electronic prescriptions. Also, the need to implement electronic signatures for healthcare professionals and ensure data interoperability and compliance to standards was underlined.

ELECTRONIC PRODUCT INFORMATION FOR HUMAN MEDICINES (ePI)

Healthcare professionals are invited to provide feedback on the draft key principles governing the electronic product information (ePI) for all human medicines authorised in the European Union (EU) that will be developed and used throughout the EU. The need to improve the summary of product characteristics (SmPC) and the package leaflet (PL) emerged in 2017 when the European Commission (EC) and the European Medicines Agency (EMA) identified the areas where SmPC and PL could be

improved to meet the needs of patients and healthcare professionals. The ePI will not eliminate, substitute or add to the current paper format, but provides the possibility of having a standardised electronic format. Therefore, the use of ePI will not constitute a new legal obligation and it will not affect Directive 2001/83/EC on medicinal products for human use.

Notable is the fact that, depending on the Member State that will decide to include the mobile technology feature on the medicine packaging, the ePI will have implications for (hospital) pharmacists. As outlined in the position of the Co-ordinated Group for Mutual Recognition and Decentralised Procedures for humans, mobile scanning technology (such as two-dimensional bar code, quick response codes and so on) will ensure that (hospital) pharmacists can access additional information on, for instance, risk minimisation material.

The envisaged benefits of ePI are the following:

- ▶ Improved dissemination and immediate update of the latest and regulator-validated information on a medicine's safety, benefits and conditions of use in all EU languages, including Norwegian and Icelandic.
- ▶ Enhanced readability, interconnectivity with present and future eHealth initiatives (electronic health records, e-prescribing and pharmacovigilance systems, the future European medicines web portal), and accessibility.
- ▶ Improved patient input in development and testing, and promoting best practices.
- ▶ Development of a standard electronic format.

The Heads of Medicines Agencies (HMA) and the EMA will develop an implementation roadmap in the future that will be based on the outcomes of this public consultation. The consultation hosted by the EMA is available on its website until 31 July 2019. Hospital pharmacists are encouraged to participate.

HTA TALKS WITH EAHP INVOLVEMENT

Part of the European Commission's (EC) initiative on strengthening European Union (EU) cooperation on Health Technology Assessment (HTA) was the expansion of the HTA Network. In addition to Member States, representatives from patient and consumer groups, health providers, payers and industry are engaging via the HTA Network Stakeholder Pool.

The aims of the HTA Network Stakeholder Pool are the following:

- ▶ To contribute to policy development related to HTA at the EU level by providing views, information and clinical expertise to the coordination group.
- ▶ To ensure that stakeholder views are reflected in the policy development in a balanced way.
- ▶ To create synergies between different stakeholders.

The European Association of Hospital Pharmacists (EAHP) is part of the health providers group. The latest HTA Network Stakeholder Pool meeting took place on 16 January 2019 in Brussels, Belgium. The discussions focused on general updates on what has been done to involve stakeholders and the activities of the European Network for Health Technology Assessment (EUnetHTA). The afternoon was dedicated to exchanges on increased patient involvement in HTA procedures, information sharing between the industry and EUnetHTA focusing on horizon scanning, early dialogue and the identification of technologies for joint assessments.

The exchange with the HTA Network Stakeholder Pool has been carried out in parallel to the EC's work on a legislative proposal for a regulation on HTA covering new medicines and medical devices that would amend Directive 2011/24/EU. The main changes point to the design of common European assessment methods, increased data and expertise sharing, and the implementation of common procedures across the EU.

UPDATES FROM THE EUROPEAN MEDICINES AGENCY IN FEBRUARY 2019

The European Medicines Agency (EMA) announced the commencement of reviews for the cancer medicine Lartruvo and a study on bleeding risk with direct oral anti-coagulants. In addition, the EMA shared information on nitrosamine impurities for sartan blood pressure medicines (also known as angiotensin II receptor blockers) and on the European Union-wide suspension of fenspiride medicines, used in children and adults to relieve cough caused by lung diseases.

Review of cancer medicine Lartruvo started

The European Medicines Agency (EMA) has started a review of the cancer medicine

Lartruvo (olaratumab) after preliminary results from the ANNOUNCE study, which was requested at the time of authorisation in 2016, became available. These show that adding Lartruvo to doxorubicin does not prolong the lives of patients with soft tissue sarcoma more than doxorubicin alone.

Based on the preliminary results of the study, the EMA has already recommended that no new patients should start treatment with the medicine, and healthcare professionals have been informed in writing of the updated treatment recommendations.

The EMA will now assess the impact of the full study results on the medicine's authorised use and recommend whether Lartruvo's marketing authorisation in the European Union should be maintained, varied or suspended.

EMA starts review of a study on bleeding risk with direct oral anticoagulants

The European Medicines Agency (EMA) is reviewing the results of a study with the direct oral anticoagulants Eliquis (apixaban), Pradaxa (dabigatran etexilate) and Xarelto (rivaroxaban). This observational study, commissioned by the EMA, assessed the risk of major bleedings with these medicines when used to prevent blood clotting in patients with non-valvular atrial fibrillation (irregular rapid contractions of the heart), in comparison with other oral anticoagulants.

Results from this study show differences in the risk of major bleedings between these medicines. They also raise concerns about the level of adherence in clinical practice to restrictions, special warnings and precautions in the medicines' product information.

The review aims to assess whether the results of this study have implications on the use of the medicines in clinical practice and whether any changes to the conditions of use and current measures to minimise the risk of bleeding would be needed.

EMA communication: sartan medicines: companies to review manufacturing processes to avoid presence of nitrosamine impurities

Companies that make sartan blood pressure medicines (also known as angiotensin II receptor blockers) are being required to review their manufacturing processes so that they do not produce nitrosamine impurities.

These recommendations follow the European Medicines Agency's (EMA) review of N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA), which are classified as probable human carcinogens (substances that could cause cancer) and have been detected in some sartan medicines.

For the vast majority of sartan medicines, impurities were either not found or were present at very low levels.

The review estimated the highest possible cancer risk with these impurities. It concluded that if 100 000 patients took valsartan from Zhejiang Huahai (where the highest levels of impurities were found) every day for 6 years at the highest dose, there could be 22 extra cases of cancer due to NDMA over the lifetimes of those 100 000 patients. NDEA in these medicines could lead to 8 extra cases in 100 000 patients taking the medicine at the highest dose every day for 4 years. The estimates have been extrapolated from animal studies and are very low compared with the lifetime risk of cancer in the European Union (one in two).

European Union-wide suspension of fenspiride medicines, used in children and adults to relieve cough caused by lung diseases

The suspension is a precautionary measure to protect patients while the Pharmacovigilance Risk Assessment Committee (PRAC) reviews the risk of QT prolongation and torsades de pointes (abnormalities of the heart's electrical activity that may lead to heart rhythm disturbances).

Cases of heart rhythm problems had been reported in patients who had taken these medicines in the past. To explore the potential link between fenspiride and these heart rhythm problems, animal studies were carried out which now show that fenspiride has the potential to prolong QT in humans.

The PRAC will now examine all the available evidence and make recommendations on the action to be taken on marketing authorisations for fenspiride medicines across the European Union. Once the review is concluded, the European Medicines Agency (EMA) will communicate further and provide updated guidance to patients and healthcare professionals.

For more information please visit the EMA's website at <https://www.ema.europa.eu/>.

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