Pre-market assessment

EMA report on adaptive pathways pilot
European Union – The EMA has published a final report on the experience gained during its pilot project on adaptive pathways. The pilot was launched in March 2014 and has now ended. The adaptive pathways approach makes use of existing regulatory tools to address unmet medical needs. A medicine will first be authorized in a small patient population that is likely to benefit most from it. Additional evidence is then gathered over time resulting in progressive licensing adaptations to extend or restrict the previously authorized indications.

Of 62 applications received during the pilot, 18 led to meetings with stakeholders, and seven of these progressed to receive further advice through the adaptive licensing route. The pilot has shown that adaptive pathways can bring multiple stakeholders together to agree on a plan to generate data on a medicine across its lifespan, particularly in areas where evidence generation is challenging. Aspects for further reflection have been identified. A stakeholder workshop on the adaptive pathways approach will be held on 8 December 2016.

Medicines developers are invited to submit proposals for adaptive licensing to the EMA. An updated guidance document has been published on the Agency’s website, outlining the steps to follow.

► EMA Press release, 3 August 2016.

Experiences in publishing assessment reports
A joint article published in Drug Discovery Today describes the positive experiences of the EMA and the TGA with the publication of assessment reports for medicines. According to the authors, increasing web traffic highlights the regulators’ success in facilitating access to information on medicines and how they are evaluated. The article concludes that European public assessment reports (EPARs) and Australian Public Assessment Reports (AusPARs) ensure high transparency about the reasons for marketing authorization of medicines, and that regulatory authorities can learn from each other when making information on medicines publicly available.


Collaboration

EMA and FDA collaborate on patient engagement
European Union, United States of America – The EMA and the FDA have set up a new working group to exchange best practices on how to involve patients in development, evaluation and post-authorization activities related to medicines.

Patients bring real-life experience as well as specific knowledge and expertise
to regulatory discussions on medicines. Their involvement is a priority for both agencies. The new cluster is expected to meet three to four times per year via teleconference. Areas for discussion will include the processes for selecting and preparing patients to take part in the agencies’ activities, ensuring that patients are independent and representative, and reporting on the impact of patient involvement.


Post-market surveillance

New EMA guidance on monitoring of biological medicines

European Union – The EMA has published a number of finalized guidance texts on its EU Good Pharmacovigilance Practices (EU-GVP) web site, including a new chapter titled Product- or population-specific considerations II: Biological medicinal products. The chapter provides guidance on how to better monitor and manage the safety of biological medicines to optimize the safe and effective use of these products in Europe.

Biological medicines contain one or more active substances made by or derived from a biological source, such as blood or plasma. The active substances of biological medicines are larger and more complex than those of non-biological medicines. The new guidance takes into account the complexity of biological medicines and their inherent variability in molecules of the same active substance, particularly in different batches of a medicine. It highlights specific issues and challenges for the pharmacovigilance of biological medicines, e.g. in relation to variability of the active substance or traceability of products, provides recommendations on how to address these specificities and challenges, and outlines the roles and responsibilities of the various actors.

The new chapter comes into force on 16 August 2016. It applies to biological medicines, biosimilars and medicines which contain the same or a closely related active substance but are not authorized as biosimilars. It does not apply to vaccines or advanced therapy medicinal products, as separate guidance already exists for these.

The EU-GVP is a key deliverable of the 2010 pharmacovigilance legislation. It applies to centrally authorized and nationally authorized medicines. An updated module on post-authorization safety studies has also been released, giving clearer guidance for these studies and distinguishing between legal obligations and recommendations.

In addition, EU-GVP draft texts on management and reporting of adverse reactions, signal management and signal detection have been published for comment.


EMA. Good pharmacovigilance practices [web site]. Updated 15 August 2016.

Report on pharmacovigilance activities in Europe

European Union – The European Commission has published a report on the pharmacovigilance activities of the European medicines regulatory network in the three years following the introduction of the new pharmacovigilance legislation in July 2012.

The creation of the Pharmacovigilance Risk Assessment Committee (PRAC) and the regulatory tools made available under the revised legislation have enabled
faster detection of safety issues. Some of the concrete achievements during the past three years include the use of risk management plans as an integral part of proactive safety management, improved reporting of side-effects with an increase by 50% in direct reports from patients, investigation of safety signals by the PRAC and prompt regulatory actions where needed, submission of periodic safety update reports (PSURs) by pharmaceutical companies for assessment of the benefit-risk balance of marketed medicines by regulators, and safety-related referrals leading to PRAC recommendations for a harmonized position across the EU.

► EMA News, 8 August 2016.

Good manufacturing practice

EMA adopts data integrity guidelines
European Union – The EMA has released new good manufacturing practice (GMP) guidance to ensure the integrity of data generated in the process of testing, manufacturing, packaging, distribution and monitoring of medicines. Regulators rely on these data to evaluate the quality, safety and efficacy of medicines and to monitor their benefit-risk profile throughout their life span.

Data integrity is key to public health protection. Controlling of data records helps ensure that the data generated are accurate and consistent to support good decision-making by both pharmaceutical manufacturers and regulatory authorities. The advice, which applies to both paper-based and electronic systems, is aligned with existing GMP guidance published by some regulatory authorities participating in the Pharmaceutical Inspection Co-operation Scheme (PIC/S). It should be read in conjunction with national guidance, medicines legislation and the GMP standards published in Eudralex volume 4.


Labelling

Improved product labels in Canada
Canada – Health Canada has released new guidance for industry on improved labels and packages that will minimize the risk of confusion. Two “Good Label and Package Practices” guides have been provided, one for over-the-counter medicines and another for prescription drugs. The guidance includes instructions for a new standardized Facts Table that will be required on the outer labels of over-the-counter drugs, with easy-to-read product information such as ingredients, directions and warnings. The requirement will be phased in from June 2017.


Antibiotics

EMA recommends reducing veterinary use of colistin
European Union – The EMA has recommended that countries should reduce the use of the last-resort antibiotic colistin in animals to decrease the risk of antimicrobial resistance. The goal is to cut colistin sales by 65%. Colistin-containing medicines should only be used as a second line treatment in animals. In addition, colistin should be reclassified into the category of antimicrobials listed by WHO as critically important to human health.
The advice updates EMA guidance from 2013 and takes into account comments made by stakeholders during a public consultation that ended on 26 June 2016. The European Commission requested this update in response to the discovery of a new mechanism of colistin resistance caused by the mcr-1 gene, which can be transferred between different types of bacteria. The gene was first identified in Enterobacteriaceae in South China, and has also been found in the EU and other regions.


Global implications of antibiotics control in India
India – Following the recent ban of around 330 fixed-dose combinations (FDCs) by the Government of India, including 63 products containing antibiotics, the authors of an article in The Lancet Global Health have urged the international community to support the full implementation of the ban, emphasizing that controlling antibiotic resistance in India is key for controlling antibiotic resistance worldwide.

Growing worldwide trade and travel has allowed resistant microorganisms to spread rapidly. New Delhi metallo-β-lactamase, an enzyme that causes bacteria to be resistant to antibiotics, was first reported in India in 2008 and is now found worldwide. Some of the banned FDCs have reportedly been exported to African and Asian countries.


Tripartite meeting on evaluation of new antibacterial agents
London – At a meeting held between the regulatory authorities of Europe, Japan and the United States on 1-2 September 2016, the three agencies discussed regulatory approaches that could stimulate the development of new antibiotics to fight antimicrobial resistance and protect global public health. They agreed that alignment of data requirements for the evaluation of new antibacterial agents can support this aim, but that some flexibility is needed where treatment options are limited due to antimicrobial resistance, and that abbreviated clinical development programmes for new antibiotics may be appropriate to address unmet needs related to antimicrobial resistance. They also identified areas of closer collaboration and coordination of efforts to encourage the development of safe and effective antibacterial treatments.

The next tripartite meeting is scheduled to take place in spring 2017.


Controlled substances
Tighter control of W-18 in Canada
Canada – The Government of Canada has published final amendments to add the synthetic, potentially harmful substance W-18 to Schedule I of the Controlled Drugs and Substances Act (CDSA) and to the Restricted Drugs section of the Food and Drug Regulations, making unauthorized activities such as production, possession, importation or exportation and trafficking illegal. There is evidence that W-18 has been used recreationally in Europe and Canada. W-18 has been found in samples falsely
labelled as legitimate medicines such as oxycodone that were seized by Canadian law enforcement authorities in 2015. (1)

Health Canada has clarified that the tightened controls were adopted in view of data published in the patent application for W-18 showing its very high activity against pain on mice, suggesting a potentially severe risk for harm. In the absence of data on the use of W-18 in humans there is no specific knowledge on its mechanisms of action, its pharmacology, or whether naloxone would be effective to reverse its effects. (2)


(2) Health Canada advisory, 13 June 2016.

Canada proposes scheduling of fentanyl precursors
Canada — Health Canada has proposed to move forward with plans to restrict six chemicals used in the production of fentanyl, to make their unauthorized importation and exportation illegal. This follows an increase in domestic production of illicit fentanyl reported by the Canadian police.

The proposed regulatory change is part of Health Canada’s opioid action plan, which was announced by the Health Minister in June 2016.


Blood safety

Shorter deferral period for MSM in Canada
Canada — Health Canada has authorized two Canadian blood operators to reduce the deferral period for blood donation for men who have sex with men (MSM) from five years to one year. The two operators had submitted scientific data which were reviewed by Health Canada and found to support the conclusion that the change would not reduce the safety to recipients of donated blood.

This change brings Canada into line with several other countries which have implemented a one-year deferral period for men who have sex with men, including the United States, Australia, New Zealand, England, Scotland and France.


All U.S. blood donations to be screened for Zika virus
United States of America — As a further safety measure against the emerging Zika virus outbreak, the FDA has issued a revised guidance recommending universal testing of donated whole blood and blood components for Zika virus in the U.S. and its territories. In earlier guidance, screening had been recommended only in areas with active Zika virus transmission.

The expanded testing will reduce the risk of Zika virus transmission.

► FDA News release, 26 August 2016.
Under discussion

United Kingdom – The MHRA has published draft data integrity guidance for industry. The guidance covers data governance systems across good practices related to the laboratory, clinical, manufacturing, distribution and pharmacovigilance areas. It addresses fundamental failures identified in regulatory inspections. The deadline for comments is 31 October 2016.

► MHRA Announcement, 21 July 2016.

European Union – The EMA has published a draft guideline on the use of innovative modelling and simulation in medicines development. The draft guideline gives detailed advice on the data that should be included in a modelling report of an application dossier, and the supportive data needed to assess a modelling platform. Comments are invited until 31 January 2017.

► EMA News, 29 July 2016.

European Union – The EMA has launched a public consultation on revised guidance regarding the development of medicines to treat tuberculosis. The guidance is an addendum to EMA’s guideline on the evaluation of medicines to treat bacterial infections. Comments can be sent to the Agency until 31 January 2017.

► EMA News, 1 August 2016.

European Union – Updated guidance texts on the management and reporting of adverse reactions, signal management and signal detection have been published for comment on the EMA good pharmacovigilance practices (GVP) website. The deadline for comment is 18 October 2016.

► EMA. Good pharmacovigilance practices [web site]. Updated 15 August 2016.

United States of America – The FDA has published two draft guidance texts on next generation sequencing (NGS) diagnostics, a new technology to scan human DNA to detect genomic variations that may point to individual health risks or help to inform treatment decisions. Public comments are invited during a 90-day comment period.

► FDA News release, 6 July 2016.

United States of America – The FDA has established a public docket and requested comments regarding options for blood donor deferral policies to reduce the risk of HIV transmission. Specifically, comments are invited on the feasibility of moving from the existing time-based deferrals to alternate options such as the use of individual risk assessment. The comment period is 120 days.

Approved

Lixisenatide for type 2 diabetes
Product name: Adlyxin®
Dosage form: Once-daily injection
Class: Glucagon-like peptide-1 (GLP-1) receptor agonist; ATC code: A10BX10
Approval: FDA
Use: Treatment of adults with type 2 diabetes.
Benefits: Improvement of haemoglobin A1c levels.
Safety information:
• Severe hypersensitivity reactions, including anaphylaxis, were reported in clinical trials.
• The FDA has required post-market studies on immunogenicity and on safety and efficacy in children.
• Lixisenatide should not be used to treat people with type 1 diabetes or patients with diabetic ketoacidosis.

Cholera vaccine
Product name: Vaxchora®
Dosage form: Oral liquid
Class: Live, attenuated cholera vaccine; ATC code: J07AE02
Approval: FDA (fast-track designation, priority review)
Use: Prevention of cholera in travellers.
Benefits: Additional cholera-prevention measure for travellers.
► FDA News release, 10 June 2016.

Lifitegrast for dry eye disease
Product name: Xiidra®
Dosage form: Ophthalmic solution
Class: Lymphocyte function-associated antigen 1 (LFA-1) antagonist
Approval: FDA
Use: Treatment of dry eye disease.
Benefits: Improvement in signs and symptoms of eye dryness.
Safety information: The safety and efficacy of lifitegrast in patients below the age of 17 years has not been studied.
► FDA News release, 12 July 2016.

Cell-based therapy to support stem cell transplant in blood cancer patients
Product name: Zalmoxis®
Dosage form: Dispersion for infusion
Class: Genetically modified allogeneic T cells
Approval: EMA (conditional approval; orphan designation)
Use: Add-on treatment in haploidentical haematopoietic stem cell transplantation of adult patients with high-risk haematological malignancies.
Benefits: Ability to increase overall survival rates.
Safety information: This product can cause graft-versus-host disease. A suicide gene in the modified T cells makes them susceptible to ganciclovir or valganciclovir. One of these medicines can therefore be given to prevent further development of the disease.

Biosimilar

Etanercept-szzs
Product name: Erelzi®
Dosage form: Injection
Biosimilar to: Enbrel® (etanercept)
Approval: FDA (approved as a biosimilar, not as an interchangeable product)
Use: Treatment of multiple inflammatory diseases.
Safety information: Etanercept-szzs should not be given to patients with sepsis.
► FDA News release, 30 August 2016.
Extensions of indications

**Emtricitabine & tenofovir disoproxil for HIV pre-exposure prophylaxis**

**Product name:** Truvada®

**Approval:** EMA recommendation

**Newly approved use:** In combination with safer sex practices, to reduce the risk of sexually-acquired human immunodeficiency virus type 1 (HIV-1) infection in adults at high risk.

**Note:** This indication was approved to enable intensification of preventive measures against HIV, given the high number of new infections worldwide.

► [EMA Press release, 22 July 2016](#).

**Cabozantib, lenvatinib approved in the EU for kidney cancer**

**Product name:** Cabometyx® (cabozantib), Kisplyx® (lenvatinib)

**Approval:** EMA recommendation (accelerated assessment)

**Newly approved use:** Treatment of advanced renal cell cancer (in the case of lenvatinib: in combination with everolimus)

**Note:** The two medicines were previously approved for thyroid cancer both in the EU and in the U.S. under the names of Cometriq® (cabozantib) and Lenvima® (lenvatinib). In the U.S., their indications were extended in April and May 2016 respectively to include advanced renal cancer.

► [EMA Press release, 22 July 2016](#).

**Interim import approval**

**Naloxone nasal spray to prevent deaths from opioid overdose**

Canada – The Canadian Minister of Health has signed an Interim Order to temporarily allow naloxone in nasal spray form to be imported from the U.S. and sold in Canada. Until now, only the injectable format of naloxone was available in Canada.

Naloxone nasal spray is under expedited review for authorization in Canada. The import order was granted to enable immediate access to easy-to-use formats of naloxone by police and family members, to help prevent deaths from opioid overdoses. An English and French instruction sheet will be provided together with the product.

► [Government of Canada News release, 6 July 2016](#).

**Diagnostics**

**Assay to detect markers for antibiotic resistance**

**Product name:** Xpert Carba-R® Assay

**Approval:** FDA

**Use:** Detection of specific genetic markers associated with carbapenemase, the enzyme produced by Carbapenem-resistant Enterobacteriaceae, in patient specimens. The test is intended to be used in conjunction with other clinical and laboratory findings.

**Benefits:** Testing of specimens from patients enables faster detection of resistance markers than testing of samples derived from bacterial cultures.

**Note:** The Xpert Carba-R® Assay tests only for genetic material. It does not detect bacteria, carbapenemase activity or other possible non-enzymatic causes of carbapenem resistance. Neither does it detect all types of carbapenemase genes. It is important to recover bacteria for accurate tracking of the spread of carbapenem resistance. Laboratories should continue to perform standard bacterial culture in conjunction with the use of the Xpert Carba-R® Assay. In addition, concomitant cultures are necessary to recover organisms for epidemiological typing, antimicrobial susceptibility testing and confirmatory bacterial identification.

► [FDA News release, 29 June 2016](#).