Regulatory action and news

Regulatory options in the fight against antimicrobial resistance
European Union – The European Medicines Agency (EMA) has published a report highlighting the outcomes of its workshop titled “Best use of medicines legislation to bring new antibiotics to patients and combat the resistance problem”. The event, held in November 2013, brought together key EU and international stakeholders. Recommendations were made in three areas:

• the effective use of the current EU regulatory framework for approval of new antibacterials, including a new evaluation guideline with a recently adopted addendum, as well as the EMA’s fee waiver system for small and medium enterprises;
• the appropriate use of antibacterials for human and veterinary use; and
• research and development, with an efficient and early dialogue between industry and EMA.


EMA and FDA collaborate on bioequivalence inspections
European Union / United States of America – The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) have launched a joint initiative to share information on inspections of bioequivalence studies submitted to participating authorities. These initially include the FDA and the regulatory authorities of France, Germany, Italy, the Netherlands and the United Kingdom. Additional EU member states are expected to join the initiative in the future.

Bioequivalence studies submitted in support of generic medicines applications must demonstrate scientifically that the generic product performs in the same manner as the innovator medicine.

The initiative, which includes an 18-month pilot phase, will be carried out in the framework of the confidentiality arrangements established between the European Commission, the EMA, interested EU Members States and the FDA. Its key objectives are to:

• streamline information-sharing on inspections of bioequivalence studies conducted and planned for generic medicines marketing authorization applications (information will be shared for clinical facilities, analytical facilities or both);
• share information on negative inspection outcomes, which reveal system problems of these facilities;
• conduct joint inspections of clinical trial sites all over the world; and
• provide training opportunities to improve bioequivalence inspections.

The initiative builds on the successful 2009 EMA-FDA Good Clinical Practice (GCP) Initiative, designed to ensure that clinical trials submitted in marketing applications for medicines in the United States and Europe are conducted ethically and that the data generated by these trials are reliable.

References:
FDA News release, 18 December 2013.
**Tafenoquine receives FDA Breakthrough Therapy designation**

**United States of America** – The US Food and Drug Administration has granted Breakthrough Therapy designation for tafenoquine, an investigational medicine for the treatment and relapse prevention of Plasmodium vivax malaria. The designation will expedite the regulatory review process of the potential new medicine, which recently completed Phase II clinical trials successfully.

**Reference:** [Medicines Venture for Malaria (MMV). Press release, 20 December 2013.](#)

---

**Regulatory action against Ranbaxy’s Toansa facility**

**United States of America** – The Food and Drug Administration (FDA) has prohibited the manufacturing site in Toansa, India of Ranbaxy Laboratories, Ltd from producing and distributing active pharmaceutical ingredients (APIs) for FDA-regulated drug products. The Toansa facility is now subject to certain terms of a consent decree of permanent injunction entered against Ranbaxy in January 2012.

The decree contains, among other things, provisions to ensure compliance with current good manufacturing practice (cGMP) requirements at Ranbaxy facilities in Paonta Sahib and Dewas, India, as well as provisions to address data integrity issues at those facilities. In September 2013, the FDA added Ranbaxy’s Mohali facility to the cGMP provisions of the decree.

The FDA’s inspection of the Toansa facility, which concluded in January 2014, identified significant cGMP violations. These included Toansa staff retesting raw materials, intermediate drug products and finished API after those items failed analytical testing and specifications in order to produce acceptable findings, and subsequently not reporting or investigating these failures.

**Reference:** [FDA News Release, 23 January 2014.](#)

---

**WHO response to FDA findings at Ranbaxy’s Toansa site**

**World Health Organization** – In response to the US Food and Drug Administration (FDA)’s findings at Ranbaxy’s Toansa facility during an unannounced inspection in January 2014, the WHO Prequalification Programme has suspended its authorization to use active pharmaceutical ingredients (APIs) from that facility in WHO-prequalified finished products. It has also suspended all assessment of Ranbaxy’s applications to prequalify APIs from the Toansa site in their own right.

WHO had requested Ranbaxy to address major deficiencies observed at the Toansa site in June 2013. As WHO has verified, since 2010 Ranbaxy has used only approved APIs from sites other than Toansa in the manufacture of the four prequalified products concerned. With international regulatory partners WHO will now ascertain supply options to avoid shortages of needed formulations.

The WHO Prequalification Programme condemns GMP practices that lead to provision of misleading information and advises buyers of medicines to consider the manufacturer’s track record and API sources before undertaking any procurement.

**Reference:** [WHO Press note. 24 January 2014](#)

---

**New partnership to strengthen regulatory systems**

**Switzerland** – The Bill & Melinda Gates Foundation, the Swiss Federal Department of Home Affairs and the
Federal Department of Foreign Affairs have signed a Memorandum of Understanding (MOU) to improve and accelerate access to medicines in resource-constrained countries. This should be achieved through cooperation to strengthen regulatory systems in these countries. The cooperation aims to increase the efficiency of the regulatory review and registration process and will initially focus on sub-Saharan countries.  


Canada-US Common Electronic Submissions Gateway
Canada - Health Canada has launched the Common Electronic Submissions Gateway (CESG), making it possible for companies to submit medicines authorization data online using a special dedicated channel of the United States Food and Drug Administration’s (US FDA) existing system. This ongoing shared mechanism was created part of ongoing work by the Canada-US Regulatory Cooperation Council to better align regulatory systems between Canada and the United States.  


Updated guidance for annual strain change of seasonal influenza vaccines
European Union – The European Medicines Agency (EMA) has updated its guidance for the annual strain change of influenza vaccines to reflect current knowledge and align it with the approaches of other regulatory authorities globally. The update introduces a system for strengthened and sustainable monitoring of an influenza vaccine’s performance over the years in a real-life setting. From the influenza season 2014-2015 onwards, vaccine manufacturers will be required to submit for each vaccine appropriate measures for proactive surveillance of the safety and effectiveness to regulatory authorities for review. From the influenza season 2015-2016, with the new system in place, EMA will longer requires routine submission of clinical trials for annual strain-change updates. EMA will publish interim guidance by March 2014 on the principles of safety monitoring commitments that should form part of the proactive surveillance.  


EMA and FDA strengthen collaboration on pharmacovigilance
European Union / United States of America – The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) have set up a new forum for monthly teleconference meetings on pharmacovigilance (medicine safety) topics. Canadian and Japanese regulatory authorities will participate as observers. This increased degree of interaction will allow the authorities to work swiftly in the area of the safety of medicines and to coordinate communication activities. The EMA and the FDA have already set up collaborative clusters to discuss issues related to biosimilars, medicines to treat cancer, orphan medicines, medicines for children and blood-based products, among other topics. The creation of the pharmacovigilance cluster is the latest step in the EMA’s and FDA’s wider approach to expand and reinforce international collaboration.  

References:  
FDA News release, 19 February 2014.
European Medicines Agency publishes first summary of a risk-management plan for a medicine
European Union – The European Medicines Agency (EMA) has published the first summary for the public of the risk management plan (RMP) of a newly authorised medicine, namely florbetaben (18F) (Neuraceq®). The summary describes what is known and not known about the medicine’s safety and states what measures will be taken to prevent or minimize its risks. EMA will pilot the publishing of RMP summaries for all newly centrally authorized medicines during 2014.

This new type of publication is a further step towards increased transparency and is one of the requirements of the new European pharmacovigilance legislation. The RMP summary complements the European public assessment report (EPAR) summary. EMA had revised the EPAR format in 2013 to provide more information on the benefit-risk balance of medicines.


EMA and FDA extend parallel assessment pilot
European Union / United States of America – The European Medicines Agency and the United States Food and Drug Administration have extended their joint pilot programme for the parallel evaluation of quality-by-design (QbD) applications until 2015. The programme promotes the consistent implementation of the concepts of ICH quality guidelines Q8, Q9, Q10 and Q11. Applicants that volunteer to make use of the programme benefit from a harmonized evaluation of the relevant parts of their submission.


Australia and New Zealand harmonization activities
Australia / New Zealand – In working towards an Australia New Zealand Therapeutic Products Agency (ANZTPA) the TGA and Medsafe embarked on a regulatory alignment programme in November 2013. Of 14 activities in the areas of medicines, active pharmaceutical ingredients, safety, medical devices and biological and blood products, two have been completed in the first quarter of 2014: New Zealand changed paediatric dosage instructions for paracetamol and ibuprofen to align with Australia, and the two authorities have published a common list of colouring substances allowed for use in medicines for oral and topical use.


Approvals

First adjuvanted vaccine for H5N1 avian influenza approved
United States of America – The Food and Drug Administration (FDA) has approved the first adjuvanted vaccine for the prevention of H5N1 influenza, commonly known as avian or bird flu, for use in people 18 years of age and older who are at increased risk of exposure to the H5N1 influenza virus. The vaccine is not intended for commercial availability. The U.S. Department of Health and Human Services has purchased it from the manufacturer for the National Stockpile for distribution by public health officials if needed.
The H5N1 component and the AS03 adjuvant component are supplied in two separate vials, which must be combined prior to use. The vaccine is administered via intramuscular injection in two doses, 21 days apart. Efficacy studies showed that 91% of individuals between the ages of 18 and 64 years and 74% of individuals 65 years and older who received the two-dose regimen developed antibodies at a level that is expected to reduce the risk of getting influenza.


**Umeclidinium and vilanterol approved for chronic obstructive pulmonary disease**

United States of America – The Food and Drug Administration (FDA) has approved umeclidinium and vilanterol inhalation powder (Anoro Ellipta®) for the once-daily, long-term maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

Umeclidinium is an anticholinergic that relaxes the muscles around the large airways, and vilanterol is a long-acting beta2-adrenergic agonist (LABA) that relaxes the muscles of the airways. LABAs increase the risk of asthma-related death. Umeclidinium and vilanterol inhalation powder is not approved for the treatment of asthma, nor should it be used to treat acute bronchospasm. Side effects can be serious and include narrowing and obstruction of the respiratory airway (paradoxical bronchospasm), cardiovascular effects, increased pressure in the eyes (acute narrow-angle glaucoma), and worsening of urinary retention.


**Dapaglifozin approved for type 2 diabetes**

United States of America – The Food and Drug Administration (FDA) has approved dapaglifozin (Farxiga®) tablets to improve glycaemic control, along with diet and exercise, in adults with type 2 diabetes.

Dapaglifozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor that blocks the reabsorption of glucose by the kidney, increases glucose excretion and lowers blood glucose levels. It has been studied as a stand-alone therapy and in combination with other type 2 diabetes therapies.

Dapaglifozin should not be used to treat patients with type 1 diabetes, with increased ketones in their blood or urine (diabetic ketoacidosis), or with renal impairment. It is not recommended for patients with active bladder cancer and should be used with caution in patients with a history of bladder cancer. Dapaglifozin can cause dehydration, especially in patients with age-related or otherwise impaired renal function and those taking diuretics.


**Trametinib and dabrafenib approved in combination for advanced melanoma**

United States of America – The Food and Drug Administration (FDA) has approved trametinib (Mekinist®) in combination with dabrafenib (Tafinlar®) to treat patients with unresectable or metastatic melanoma. This follows the approval of the two medicines as single agents in May 2013. The combination was approved under the FDA’s Accelerated Approval Program.

Droxidopa approved for neurogenic orthostatic hypotension
United States of America – The Food and Drug Administration (FDA) has approved droxidopa (Northera®) capsules for the treatment of neurogenic orthostatic hypotension, a rare, chronic and often debilitating drop in blood pressure upon standing that is associated with Parkinson’s disease, multiple-system atrophy, and pure autonomic failure. Droxidopa was approved under the FDA’s accelerated approval programme and received orphan-product designation.

The product carries a warning about the risk of increased blood pressure while lying down (supine hypertension), a common problem that affects people with primary autonomic failure and can cause stroke. Patients must sleep with their upper body elevated. Supine blood pressure should be monitored before and during treatment.


Bedaquiline recommended for approval to treat multidrug-resistant tuberculosis
European Union – The European Medicines Agency (EMA)’s Committee for Medicinal Products for Human Use (CHMP) has recommended granting a conditional marketing authorization for bedaquiline (Sirturo®) for use in combination therapy for pulmonary multidrug-resistant tuberculosis in adults when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

In recent years, the burden of tuberculosis resistant to first-line therapy has increased rapidly in the absence of new treatment options. Bedaquiline is the first representative of a new class of medicines against mycobacteria. It has received the third positive opinion recently granted by the CHMP for a medicine to treat multidrug-resistant tuberculosis, after the November 2013 recommendations for delamanid (also for a conditional approval) and para-aminosalicylic acid.


Metreleptin approved to treat rare metabolic disease
United States of America – The Food and Drug Administration (FDA) has approved metreleptin for injection (Myalept®) as replacement therapy to treat the complications of leptin deficiency in patients with generalized lipodystrophy of both the congenital and the acquired type. These complications include severe insulin resistance at a young age, diabetes mellitus that is difficult to control, and hypertriglyceridaemia.

Because of the risk of development of anti-drug antibodies, as well as the risk of T-cell lymphoma in patients with acquired generalized lipodystrophy, metreleptin is available only through a designated treatment programme.

Metreleptin is contraindicated in patients with general obesity. It is not approved for use in patients with HIV-related lipodystrophy or those with metabolic disease, including diabetes mellitus and hypertriglyceridaemia, without concurrent evidence of generalized lipodystrophy.