Regulatory news

Data-sharing

EMA Board agrees on clinical trial data-sharing policy
European Union – The EMA Management Board has reached agreement on its policy on publication of clinical trial data, together with more user-friendly amendments (1). The policy will allow EMA to proactively publish clinical trial data for downloading, saving and printing for academic and non-commercial research purposes. It is expected to become effective from 1 October 2014. Importantly, it will not prejudice citizens’ rights under existing access to documents legislation and the new clinical trials regulation.

In a separate process, EMA is now making summaries of the results of clinical trials publicly available (2). From 21 July 2014 applicants are required to upload summary results to the newly upgraded European Clinical Trials Database (EudraCT), from where the result-related information is fed into the EU Clinical Trials Register. Information on clinical trial protocols in third countries is also uploaded to EudraCT if the trials are included in a Paediatric Investigation Plan (PIP), submitted by applicants early in product development to show how a medicine will be studied in children. In July 2014, EMA started publishing PIPs on its website (3).

► (1) EMA News, 12 June 2014
   (2) EMA News 19 June 2014.

Canada advances transparency legislation
Canada – The Government of Canada has welcomed transparency amendments in a proposed patient safety law named Vanessa’s Law (Bill C-17). The amendments provide for disclosure of both positive and negative drug authorization decisions, and clinical trial information and possible disclosure of confidential business information on products that may pose a serious risk to Canadians.

Bill C-17 has been passed in the House of Commons and moves to the Senate for consideration. The amendments would strengthen Health Canada’s Regulatory Transparency and Openness Framework announced in April 2014.


FDA launches public data access platform
United States of America – The FDA has launched openFDA, a new initiative to make it easier for the public to access large public health datasets collected by the agency. The data will be provided in a structured, computer-readable format enabling searches, queries and downloads of public information directly from FDA datasets.

The initial pilot version of openFDA provides access to anonymized reports on drug adverse events and medication errors submitted to the FDA from 2004 to 2013. The pilot will later be expanded to include the FDA’s databases on product
recalls and product labeling. Additional public datasets may follow.

► FDA News release, 2 June 2014. openFDA can be accessed at: https://open.fda.gov/

Generics

Generic registration information-sharing pilot launched

European Union – The European Union’s decentralized procedure – which serves to authorize certain medicines in parallel in more than one EU Member State – is being used as a model to accelerate the assessment of applications for generic medicines as part of the International Generic Drug Regulators Pilot (IGDRP). If an applicant wishes to market the same generic product in the EU through the decentralized procedure and in other jurisdictions that form part of the pilot, the EU will share its assessment reports in real time with collaborating authorities outside the EU. This should enable medicines to be authorized in different territories in a coordinated way at approximately the same time. (1)

The first phase of the pilot will involve the EU, Australia (2), Canada, Chinese Taipei and Switzerland (3). IGDRP members that may decide to take part at a later stage include Brazil, China, Japan, Korea, Mexico, New Zealand, Russia, Singapore and South Africa. The European Directorate for the Quality of Medicines & Healthcare (EDQM) and WHO participate as observers.


More information on the IGDRP: The International Generic Drug Regulators Pilot. WHO Drug Information. 28(1); 2014:3-10.

Regulatory oversight

Canada implements labelling changes for opioids, adopts plain language labelling regulations

Canada – The Government of Canada is implementing new labelling provisions for all classes of controlled and extended release non-generic opioid pain medicines, with standardized wording that more clearly outlines safety concerns for children from accidental exposure and for newborns exposed during pregnancy. The wording also provides clearer prescriber guidance on the use of opioids, which are indicated for daily, long-term management of opioid-responsive severe pain for which alternative treatment is not adequate. Similar label changes will soon be implemented for generic opioids. (1)

Under its Plain Language Labelling Initiative, the government has also finalized new regulations for all medicines, to be phased in gradually. Key safeguards include clear wording on labels and packaging; a standardized format for non-prescription medicines labels; mandatory contact information on labels; mandatory provision by manufacturers of label and packaging mock-ups for Health Canada review; and “Look Alike - Sound Alike” provisions for manufacturers to provide evidence that their product names will not be confused with those of other authorized products. (2)


FDA outlines expectations for medicines compounding

United States of America – The FDA has issued several policy documents to support the implementation of new
compounding provisions enacted into law in November 2013.

The new law distinguishes between two types of compounding operations: Section 503A applies to pharmacies that do small compounding operations mainly in response to prescriptions, while Section 503B applies to outsourcing facilities that compound large quantities of sterile products without prescription to cater for a lack or shortage of FDA-approved finished products.

Four policy documents have been published for comment: A draft interim guidance text on GMP expectations under Section 503B with a focus on sterility and general patient safety, a rule that would modify the list of drugs which may not be compounded at all, and two revised requests for nomination of active pharmaceutical ingredients that may be used to compound products under each of the two sections.

► FDA News release, 1 July 2014.

FDA proposes new guidance for certain types of diagnostics
United States of America – The FDA has taken two steps to strengthen its oversight over certain diagnostic tests.

Firstly, the Agency has issued a final guidance on the development, review and approval or clearance of companion diagnostics. These are diagnostic tests designed to guide decisions on treatment with specific medicines for individual patients, for example in certain types of cancer. The guidance aims to foster early coordinated development of medicines and their companion tests.

Secondly, the FDA has given the legally required notice of its intention to publish a proposed risk-based oversight framework for tests which are designed, manufactured and used within a single laboratory. The guidance proposes to enforce a pre-market review for certain laboratory-developed tests (LDTs), starting with those that have the same intended use as FDA-approved or cleared companion diagnostics marketed by conventional manufacturers. However, the framework would not be extended to low-risk LDTs, LDTs for rare diseases and, under certain circumstances, LDTs for which there is no FDA-approved or FDA-cleared test.


Orphan medicines

Canada pilot project seeks patient perspectives on orphan medicines
Canada – As part of its Orphan Drug Framework to spur innovation and research, Health Canada is embarking on a pilot project that will simulate how input from patients will be gathered and incorporated into the review process for orphan medicines.

Two manufacturers have agreed to participate with their registration submissions for new medicines intended to treat chronic lymphocytic leukaemia and urea cycle disorders respectively. Patients will be asked to comment on how these disease affect their day-to-day lives, what treatments are currently available to them, what therapeutic benefits are most important to them, and what risks they are willing to take with new treatments. Once implemented, this process will ensure that patient perspectives are considered in future orphan medicine authorizations.

Submitted for approval

Malaria vaccine
Product name: RTS,S
Submitted to: EMA (Article 58 procedure for intended use outside the EU)
Intended use: Prevention of infection with *Plasmodium falciparum*. In the phase III efficacy trial, RTS,S was administered in three doses, one month apart.
Benefits: In the 18 months efficacy trial the vaccine prevented many cases of clinical and severe malaria. The highest impact was found in areas with the greatest malaria incidence. The vaccine efficacy was higher in children than in infants. To date there is no licensed vaccine available for the prevention of malaria. An effective vaccine for use alongside other measures such as bednets and antimalarial medicines would represent an advance in malaria control.

Approved

Inhaled insulin (human) for diabetes
Product name: Afrezza® Inhalation Powder
Class: Rapid-acting inhaled insulin;
ATC code: A10AF01
Approval: FDA
Use: Improvement of glycaemic control in adults with diabetes mellitus. The product is administered at the beginning of each meal. In patients with type 1 diabetes it must be used in combination with long-acting insulin.
Safety information: Due to a serious risk of acute bronchospasm in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease, the product should not be used in these patients. It is not recommended for the treatment of diabetic ketoacidosis, or in patients who smoke. The product was approved with a risk evaluation and mitigation strategy and with requirements for post-marketing studies.

Eliglustat for Gaucher disease
Product name: Cerdelga®
Class: glucosylceramide synthase inhibitor;
ATC code: A16AX10
Approval: FDA (orphan drug designation)
Use: Long-term treatment of adult patients with Type 1 Gaucher disease, a rare genetic disorder causing fatty materials to collect in the spleen.
Benefits: Additional treatment option; equally safe and effective as enzyme replacement therapy in stabilizing haemoglobin level, platelet count and spleen and liver volume.
► FDA News release, 19 August 2014.

Recombinant antihaemophilic factor for haemophilia A
Product name: Eloctate®
Class: Recombinant antihaemophilic factor, Fc fusion protein (first-in-class)
Approval: FDA (orphan designation)
Use: To control and prevent bleeding episodes, manage bleeding during surgical procedures, and to prevent or reduce the frequency of bleeding episodes in adults and children with haemophilia A.
Benefits: This recombinant product lasts longer than other Factor VIII products in the patient's blood, requiring less frequent injections for prophylaxis.
► FDA News release, 6 June 2014.

Daclatasvir for chronic hepatitis C
Product name: Daklinza®
Class: NS5A inhibitor (first-in-class);
ATC code: J05AX14
Approval: EMA (accelerated assessment)
Use: Treatment of chronic hepatitis C virus infection in adults, in combination with other medicines.
Benefits: Interferon-based combination therapies for hepatitis C have potentially serious side effects that can be difficult to manage. Daclatasvir has been shown to be effective in combination with sofosbuvir
with or without ribavirin, providing an interferon-free treatment option for hepatitis C.

**Dolutegravir / abacavir / lamivudine fixed-dose combination for HIV**

**Product name:** Triumeq®
Dolutegravir / abacavir / lamivudine 50 / 600 / 300 mg fixed-dose combination

**Class:** Antivirals for treatment of HIV infections; ATC code: J05AR13

**Approval:** EMA

**Use:** Treatment of Human Immunodeficiency Virus (HIV)-infected adults and adolescents above 12 years of age weighing at least 40 kg.

**Benefits:** Potent antiretroviral response, with a high barrier to resistance in a once-daily, single pill regimen

**Safety information:** Should not be used in patients known to carry the HLA-B*5701 allele (a genetic marker indicating a high risk of abacavir hypersensitivity)
► EMA/CHMP Summary of opinion, 26 June 2014.

**Tedizolid phosphate for skin infections**

**Product name:** Sivextro®

**Class:** Oxazolidinone antibacterial

**Approval:** FDA (expedited review under Qualified Infectious Disease Product designation)

**Use:** Treatment of acute bacterial skin and skin structure infections in adults. The product is available for intravenous and oral use.

**Benefits:** Additional treatment options against skin infections caused by *Staphylococcus aureus* (including methicillin-resistant and -susceptible strains), various *Streptococcus* species, and *Enterococcus faecalis*.

**Safety information:** The safety and efficacy of tedizolid phosphate have not been evaluated in patients with decreased levels of white blood cells (neutropenia). Alternative therapies should be considered in these patients.
► FDA News release, 6 August 2014.

**Oritavancin for skin infections**

**Product name:** Orbachiv®

**Class:** Glycopeptide antibacterial; ATC code: J01XA05

**Approval:** FDA; priority review due to Qualified Infectious Disease Product (QIDP) designation

**Use:** Intravenous treatment of acute bacterial skin and skin structure infections caused by certain susceptible bacteria, including *Staphylococcus aureus* (both methicillin-susceptible and methicillin-resistant strains), various *Streptococcus* species and *Enterococcus faecalis*.

**Benefits:** Additional treatment option for the above-mentioned, serious infections.

**Safety information:** The product information includes a warning about interference of oritavancin with coagulation tests and interaction with warfarin.
► FDA News release, 6 August 2014.

**Belinostat for peripheral T-cell lymphoma**

**Product name:** Beleodaq®

**Class:** Antineoplastic agent

**Approval:** FDA (accelerated approval; orphan designation)

**Use:** Treatment of peripheral T-cell lymphoma, a rare and fast-growing type of non-Hodgkin lymphoma.

**Benefits:** Additional treatment option for patients who had relapses or did not respond to previous treatment.
► FDA News release, 3 July 2014.

**Ibrutinib for blood cancers**

**Product name:** Imbruvica®

**Class:** Antineoplastic agent; ATC code: L01XE27

**Approval:** FDA (new indication, breakthrough therapy); EMA (orphan medicine)

**Uses:** Treatment of chronic lymphocytic leukaemia in patients with a specific genetic mutation; treatment of relapsed or refractory mantle cell lymphoma
Benefits: Longer progression-free survival and overall survival periods.

Idelalisib for blood cancers
Product name: Zydelig®
Class: Antineoplastic agent;
ATC Code: L01XX47
Approval: FDA (orphan designation, breakthrough therapy); EMA
Uses: Treatment of blood cancers, including relapsed chronic lymphocytic leukaemia, in combination with rituximab; refractory follicular lymphoma; and relapsed small lymphocytic lymphoma after at least two systemic therapies
Benefits: Longer progression-free survival in chronic lymphocytic leukaemia; improved response rate and response duration in follicular lymphoma.
Safety information: Risk of fatal and serious toxicities including liver toxicity, diarrhoea and colon inflammation, lung inflammation and intestinal perforation. The FDA approved the product with a Boxed Warning and with a Risk Evaluation and Mitigation Strategy; the EMA required the implementation of a pharmacovigilance plan.
► FDA News releases, 23 July 2014.

Bevacizumab for late-stage cervical cancer
Product name: Avastin®
Class: Antiangiogenic agent, monoclonal antibody; ATC code: L01XC07
Approval: FDA, new indication (priority review)
Use: Treatment of persistent, recurrent or late-stage (metastatic) cervical cancer in combination with other medicines.
Benefits: Increased overall survival time, compared with chemotherapy alone.
Safety information: Bevacizumab can cause perforations of the gastrointestinal tract or abnormal openings between the gastrointestinal tract and vagina.
► FDA News release, 14 August 2014.

Suvorexant for insomnia
Product name: Belsomra®
Class: Orexin receptor antagonist (first-in-class)
Approval: FDA
Use: Treatment of insomnia
Benefits: Effective compared to placebo.
Safety information: Patients using the highest strength (20 mg) should be cautioned against next-day driving or activities requiring full mental alertness. Lower doses can also impair next-day alertness as there is individual variation in sensitivity to the drug. People can be impaired even when they feel fully awake. The product will be dispensed with an FDA-approved patient medication guide. It has been classified as a controlled substance because it can be abused or lead to dependence.
► FDA News release, 13 August 2014.

Olodaterol for chronic obstructive pulmonary disease (COPD)
Product name: Striverdi Respimat® Inhalation spray
Class: Long-acting beta-adrenergic agonist (LABA); ATC code: R03AC19
Approval: FDA
Use: Long-term treatment of COPD, including chronic bronchitis and/or emphysema
Benefits: Additional long-term maintenance treatment option for patients with chronic airway obstruction
Safety information: Olodaterol carries a Boxed Warning stating that LABAs increase the risk of asthma-related death. Its safety and effectiveness in people with asthma has not been established, and it is not approved to treat asthma. It should not be used to treat acute breathing problems, or in patients with acutely deteriorating COPD. Serious potential side effects include paradoxical bronchospasm and cardiovascular effects. The FDA approved the product with a patient medication guide.
Technetium 99m tilmanocept for diagnosis in cancers
Product name: Lymphoseek®
Class: Diagnostic radiopharmaceutical agent; ATC code: V09IA09
Approval: FDA (new indication) EMA (initial authorization)
Use: FDA: To guide lymph node biopsy in the head and neck region in patients with squamous cell carcinoma. (Approved in 2013 to assist in the localization of lymph nodes draining a primary tumour in patients with breast cancer or melanoma.) EMA: Imaging and intraoperative detection of sentinel lymph nodes draining a primary tumour in adult patients with breast cancer, melanoma, or localised squamous cell carcinoma of the oral cavity. External imaging and intraoperative evaluation may be performed using a gamma detection device.
Benefits: Ability to detect tumour-draining sentinel nodes, allowing for the option of more limited lymph node surgery in patients with lymph nodes that are found to be negative for cancer.
► FDA News release, 13 June 2014.
► EMA/CHMP Summary of opinion, 25 September 2014.

Flutemetamol (18F) for diagnosis of Alzheimer’s disease
Product name: Vizamyl®
Class: Diagnostic radiopharmaceutical agent; ATC code: V09AX04
Approval: EMA
Use: Diagnosis of patients investigated for Alzheimer’s disease. Injected flutemetamol binds to amyloid neuritic plaques in the human brain which can then be seen by positron emitting tomography (PET). The product should be prescribed by clinicians experienced in the clinical management of neurodegenerative disorders.
Benefits: Flutemetamol can help detect with a high accuracy the beta-amyloid deposition, and therefore contribute valuable additional diagnostic information in Alzheimer’s disease.
► EMA/CHMP Summary of opinion, 26 June 2014.

Withdrawn applications

<table>
<thead>
<tr>
<th>Submission</th>
<th>Applicant’s reason for withdrawal</th>
<th>Reviewing authority reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faldaprevir for treatment of hepatitis C Submitted to EMA (orphan designation)</td>
<td>Since several new treatments for hepatitis C had become available after the application was first made, there was no longer an unmet medical need for such a medicine.</td>
<td>► EMA. Questions and answers on the withdrawal of the marketing authorisation application for Faldaprevir Boehringer Ingelheim (faldaprevir). 27 June 2014.</td>
</tr>
<tr>
<td>Vintafolide, with diagnostic medicines etarfolatide and folic acid, for treatment of ovarian cancer Submitted to EMA (orphan designation)</td>
<td>The preliminary data from the study could not confirm the benefit of vintafolatide in ovarian cancer patients, and confirmatory data cannot be provided since the study has been terminated.</td>
<td>► EMA. Questions and answers on the withdrawal of the marketing authorisation application for Vynfinit (vintafolide). 23 May 2014.</td>
</tr>
</tbody>
</table>