Regulatory news

Pre-market assessment

Orphan medicines approvals
European Union – The EMA has started publishing its assessment reports on whether a product still fulfils the criteria for orphan designation at the time of its marketing authorization.

To qualify for orphan designation a medicine must target a disease that is life-threatening or chronically debilitating and affects less than 5 in 10 000 patients in the EU. If another treatment is available for that rare disease, the applicant must show that the new medicine offers a clinically relevant advantage or a major contribution to patients. Orphan medicines benefit from a number of incentives, including fee reductions for scientific advice during development and ten years of market exclusivity if the orphan status is maintained once the medicine is authorized.

Publication of the orphan maintenance assessment reports will increase transparency and may provide useful information for health technology assessment bodies in establishing the cost-effectiveness of a product. The reports will be published for all positive and negative opinions as well as withdrawals as part of the European Public Assessment Reports (EPARs) for medicines. Information of a commercially confidential nature will be deleted.\(^1\)

An estimated 30 million people in the EU are affected by one of over 6 000 rare diseases. The EU’s orphan designation programme was launched in the year 2000 to incentivize research and development of medicines for these rare diseases. To date, over 1 900 medicines have been designated as orphan medicines, of which over 140 were on the market at the end of 2017.\(^2\)

\(^1\) EMA News, 17 January 2018.
\(^2\) EMA News, 21 December 2017.

United States of America – Metrics on requests for FDA orphan drug designations and approvals of requests and products since 1983 have been published on web. In the past 35 years the FDA has approved nearly 4 500 orphan drug designations in response to more than 6 300 orphan drug designation requests received, and has granted more than 650 marketing authorizations for orphan medicines.

\(^3\) FDA Law Blog post, 28 February 2018.

U.S.: Clinical data summary pilot
United States of America – The FDA has launched a pilot programme in which it will disclose parts of the clinical study reports, the summaries from the pivotal clinical trials submitted to the FDA for approval of a product. Specifically, the study report body, the protocol and amendments, and the statistical analysis plan for each pivotal study will be posted. Patient privacy and confidential commercial information in the CSRs will be protected. The pilot will include up to nine recently approved new drug applications across a range of diseases. Participation by sponsors is voluntary. The first product for which information has been posted is apalutamide, a newly approved treatment for prostate cancer.
The pilot is intended to create more transparency regarding the clinical evidence supporting marketing authorization applications and the FDA’s decision-making process. Public feedback will be sought once the pilot is complete.

Secondly, the FDA will include in the published materials relating to future approvals the identifier number from the National Institutes of Health’s clinical trial register, ClinicalTrials.gov (the NCT#). This will enable the public to link the information on clinical research on a medicine to the FDA communications published throughout the regulatory process.


**U.S.: Priority reviews for medicines needed by armed forces**

United States of America – Utilizing legal changes enacted in December 2017 the FDA will expedite its review of priority products to diagnose, treat, or prevent serious or life-threatening conditions that affect American military personnel, in a manner similar to products under the breakthrough designation programme.

Current high-priority products include freeze-dried plasma, cold-stored platelets, and cryopreserved platelets. The initial phase of the programme will therefore be conducted by the FDA’s Center for Biologics Evaluation and Research (CBER) and Department of Defense’s (DoD) Office of Health Affairs. As a broad and evolving range of medical products will be needed for service members, the programme will ultimately extend across the FDA’s capabilities.


**Biosimilars**

**Switzerland: Additional biological comparators allowed**

Switzerland – Swissmedic will now accept reference products from additional countries for studies on comparability of biosimilars. For main studies, reference products from the U.S. are acceptable in addition to those from Switzerland and the EU. For supplementary studies, comparator products from Canada are now accepted, in addition to those from Switzerland, the EU and Japan. Furthermore, environmental risk assessments (ERA) are now compulsory for biosimilar submissions to Swissmedic. (1) The question-and-answer document on authorization of biosimilars has been updated. (2)

► Swissmedic statement, 1 January 2018.

Questions and answers concerning the authorisation of similar biological medicinal products (biosimilars). Updated 9 January 2018.

**Australia: No suffixes for biosimilar names**

Australia – Following a public consultation conducted in 2017, the active ingredient of a biosimilar will continue to be designated by the Australian biological name (ABN) without a product-specific suffix. The TGA has updated its guidance on registration of biosimilars accordingly.

Collaboration

U.S. and EU to re-focus inspection resources

The beginning of November 2017 marked a milestone in implementing the mutual recognition agreement (MRA) between the EU and the U.S. Completed assessments of each other’s inspection capabilities enabled eight regulatory authorities located in the EU and the FDA to recognize the outcomes of each other’s inspections. (1) While the EU has six existing MRAs with authorities outside the Union, (2) this is a first for the FDA.

The agreement will change the frequency of inspections that the participating authorities conduct in different parts of the world. In 2011–15 about 40% of the FDA’s foreign pharmaceutical manufacturing site inspections were performed in the EU. Only about 5% of these inspections gave rise to official action, compared with 14% of the FDA’s inspections conducted in India and 21% of those conducted in China. (3) Observers expect that over the next three to five years, both the FDA and the EU will shift their resources away from each other’s territories towards facilities in India and China, and are recommending that pharmaceutical manufacturing sites operating in those countries should start preparing now for that increased scrutiny. (4)


► (2) EMA. Mutual recognition agreements [webpage].

► (3) The Mutual Reliance Initiative: A New World for Pharmaceutical Inspections. Presentation by Dara A. Corrigan at the Food and Drug Law Institute’s Annual Conference. 5 May 2017.


“3Rs”

First EMA report on actions for more ethical animal use

European Union – The EMA has published its first report summarizing the Agency’s actions to support the 3Rs principles for more ethical use of animals. “3Rs” is an acronym for replacement, reduction and refinement of animal tests. The actions described in the report are driven by the Joint CVMP/CHMP 3Rs Working Group that advises the relevant EMA committees on matters concerning the use of animals in regulatory testing of medicines.

Two new guidelines developed by the working group have been adopted, encouraging proposals for alternative testing approaches and providing guidance to individual laboratories in collaborative trials. The group also coordinates public consultations, and reviews animal tests included in lot release specifications for centrally authorized vaccines and biologicals to check compliance with current Ph.Eur monographs and to ensure that best practice in 3Rs is applied.

► EMA Press release, 28 February 2018.

United States of America – The FDA has published draft updated guidance on issuance of public warnings and notification of recalls. The draft guidance clarifies and supplements existing policy for industry and FDA staff.
Closing date: 20 March 2018.

United States of America – The FDA has proposed a risk-based enforcement approach to homoeopathic products. The new approach addresses situations where homoeopathic treatments are being marketed for serious conditions but have not been shown to offer clinical benefits, or where products labelled as homoeopathic contain potentially harmful ingredients or do not meet current good manufacturing practices.(1)

The FDA continues to find that some homoeopathic products are manufactured with active ingredients that can create health risks while delivering no proven medical benefits. For example, in January FDA testing found elevated amounts of belladonna in homoeopathic teething products. Belladonna alkaloids can have unpredictable and potentially serious adverse effects in young children. The company did not initially agree to conduct a recall. The FDA recommended that consumers stop buying these products immediately, dispose of any in their possession, and seek medical care immediately if they observe any adverse effects in their child after use of a homoeopathic teething product.(2)
► (1) FDA News Release, 18 December 2017.
Federal Register Notice, 20 December 2017.
Closing date: 20 March 2018.

European Union – The European Commission (EC), WHO and the Pharmaceutical Inspection Co-operation Scheme (PIC/S), have jointly proposed a revised version of the guidelines on manufacture of sterile medicinal products. The document is subject to parallel public consultation by the three entities.
Closing date: 20 March 2018.

United States of America – The FDA has announced the availability of draft guidance for industry on Drug products, including biological products, that contain nanomaterials.
► Federal Register Notice, 18 December 2017.
Closing date: 19 March 2018.
Approved

**Glibenclamide paediatric formulation for neonatal diabetes**

**Product name:** Amglidia®

**Dosage form:** Oral suspension

**Class:** sulfonylurea; **ATC code:** A10BB01

**Approval:** EMA (orphan designation)

**Use:** Treatment of neonatal diabetes mellitus, for use in newborns, infants and children

**Benefits:** New formulation, allowing a more accurate dosing in children. In a clinical study glycaemic control remained stable after switching from crushed tablets to oral suspension.

**Note:** Neonatal diabetes is an extremely rare form of diabetes that is diagnosed in the first six months of life. It is life-threatening and debilitating because of the symptoms caused by high blood sugar levels and the risk of ketoacidosis. This product is the first EMA-approved medicine to treat neonatal diabetes.


**Ertugliflozin for type 2 diabetes**

**Product names:** Steglatro® (ertugliflozin); Segluromet® (ertugliflozin and metformin hydrochloride); Steglujan® (ertugliflozin and sitagliptin)

**Dosage form:** Tablet

**Class:** Ertugliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor; **ATC code:** A10BK04

**Approval:** FDA, EMA

**Use:** As an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

**Benefits:** Additional treatment option for type 2 diabetes mellitus

**Safety information:** Potential adverse events include hypotension, ketoacidosis, acute kidney injury and impairment in renal function, urosepsis and pyelonephritis, lower limb amputation, hypoglycaemia, genital mycotic infections and increased LDL-C levels.


**Velmanase alfa for a rare genetic disorder**

**Product name:** Lamzede®

**Dosage form:** Powder for solution for infusion

**Class:** Recombinant human alpha mannosidase, intravenous enzyme replacement therapy; **ATC code:** A16AB15

**Approval:** EMA (marketing authorization under exceptional circumstances; orphan designation)

**Use:** Treatment of non-neurological manifestations of alpha-mannosidosis in patients with a mild to moderate form of the disorder.

**Benefits:** Decrease of serum oligosaccharide to normal levels observed in a clinical trial, with improved exercise capacity and lung function in some patients.

**Note:** Alpha-mannosidosis is a rare inherited enzyme disorder that causes cell damage in many organs and tissues. There is currently no cure for this disorder. Patients with early onset severe and rapid progressive disease often do not survive beyond childhood. Those with less severe forms of the disease are managed with supportive care.

► EMA Press release, 26 January 2018.

**Synthetic human angiotensin II for dangerously low blood pressure**

**Product name:** Giapreza®

**Dosage form:** Injection for intravenous infusion

**Class:** Vasoconstrictor

**Approval:** FDA (priority review)
Use: To increase blood pressure in adults with septic or other distributive shock

Benefits: Effective in increasing blood pressure when added to conventional treatments used to raise blood pressure.

Safety information: The product can cause clots in arteries and veins, including deep venous thrombosis, with serious consequences. Prophylactic treatment for blood clots should be used.

► FDA News release, 21 December 2017.

**Ozenoxacin for impetigo**

**Product name:** Xepi®

**Dosage form:** Cream for topical use; *ATC code:* D06AX14

**Class:** Quinolone antimicrobial

**Approval:** FDA

**Use:** Treatment of impetigo caused by *Staphylococcus aureus* or *Streptococcus pyogenes*.

**Benefits:** More effective than placebo against clinical signs and symptoms of impetigo

► Prescribing information for Xepi®, revised 12/2017.

**Hydrocortisone granules for a rare disease in children**

**Product name:** Alkindi®

**Dosage form:** Granules in capsules for opening

**Approval:** EMA paediatric-use marketing authorization (PUMA)

**Use:** Treatment of primary adrenal insufficiency, a rare hormonal disorder in infants, children and adolescents.

**Benefits:** More accurate dosing of hydrocortisone in children, with a better masking of the bitter taste.

**Note:** PUMAs can be granted for medicines which are authorized but no longer under patent protection.


**Bictegravir, emtricitabine and tenofovir alafenamide for HIV infection**

**Product name:** Biktarvy®

**Dosage form:** Once-daily fixed-dose combination tablet

**Class:** Combination of an HIV-1 integrase strand transfer inhibitor (bictegravir) and two HIV-1 nucleoside analog reverse transcriptase inhibitors (emtricitabine and tenofovir alafenamide); *ATC code:* J05AR20

**Approval:** FDA (priority review designation)

**Use:** Treatment of HIV-1 infection in adults ARV-naïve adults or those who are on a stable antiretroviral regimen for at least 3 months with less than 50 HIV-1 RNA copies per mL, no history of treatment failure and no known substitutions associated with resistance to the individual components of this product.

**Benefits:** Effective new treatment option for a range of patients with HIV-1 infection.

**Safety information:** Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate, and may occur with discontinuation of this new fixed-dose combination. Liver function should be closely monitored in these patients.

► FDA Prescribing information, revised February 2018.

**Ibalizumab for multidrug-resistant HIV infection**

**Nonproprietary name in the U.S.:** ibalizumab-uiyk

**Product name:** Trogarzo®

**Dosage form:** Injection for intravenous use

**Class:** Antiretroviral (ARV); CD4-directed post-attachment inhibitor (first-in-class)

**Approval:** FDA (fast-track designation, breakthrough therapy, priority review; orphan drug designation)

**Use:** In combination with other ARV(s), treatment of heavily treatment-experienced patients with multidrug-resistant HIV-1 infection failing their current ARV regimen.
Approved

**Benefits**: Ability to achieve a significant decrease in HIV-RNA levels in patients who have run out of other HIV treatment options.

**Safety information**: Severe side effects in clinical trials included rash and immune reconstitution syndrome.

► [FDA News release, 6 March 2018](#).

**Baloxavir marboxil** one-dose treatment for influenza

**Product name**: Xofluza®

**Dosage form**: Tablet

**Class**: cap-dependent endonuclease inhibitor

**Approval**: Ministry of Health, Labour and Welfare (MHLW) of Japan

**Use**: Treatment of influenza types A and B

**Benefits**: Treatment requires only a single oral dose regardless of age.

► [Shionogi & Co. Ltd Press release, 23 February 2018](#).

**Apalutamide** for prostate cancer

**Product name**: Erleada®

**Dosage form**: Tablets

**Class**: Androgen receptor inhibitor

**Approval**: FDA (priority review)

**Use**: Treatment of non-metastastic, castration-resistant prostate cancer

**Benefits**: Significantly longer median metastasis-free survival than with placebo

**Safety information**: Severe side effects include falls, fractures and seizures. Patients with female partners of reproductive potential should be advised to use effective contraception.

**Notes**: This is the first FDA-approved treatment for this condition, and the first to be approved based on the endpoint of metastasis-free survival.

The marketing authorization holder of this product is the first participant in the FDA's clinical data summary pilot programme (see page 28), which aims to increase transparency on the clinical evidence and decision-making process for FDA-approved products.

► [FDA News release, 14 February 2018](#).

**Burosumab** for a rare bone disease

**Product name**: Crysvita®

**Dosage form**: Solution for injection

**Class**: Human monoclonal antibody that binds to fibroblast growth factor 23 inhibiting its activity; **ATC code**: M05BX05.

**Approval**: EMA (conditional marketing authorization; orphan designation)

**Use**: Treatment of X-linked hypophosphataemia (XLH) with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons.

**Benefits**: Ability to reduce the loss of phosphate, to improve abnormally low serum phosphate concentrations and other metabolic changes, and to reduce the severity of rickets as shown in x-rays.

► [EMA Press release, 15 December 2017](#).

**Tezacaftor and ivacaftor** for cystic fibrosis

**Product name**: Symdeko®

**Dosage form**: Co-packed tablets

**Class**: Respiratory system agents; **ATC code**: R07AX31

**Approval**: FDA

**Use**: Treatment of patients with cystic fibrosis aged 12 years and older who have certain mutations.

**Benefits**: Improvements in lung function and other measures of disease.

► [Prescribing information for Symdeko®, Revised 2/2018](#).

**Netarsudil** to reduce intraocular pressure

**Product name**: Rhopressa®

**Dosage form**: Ophthalmic solution for topical ophthalmic use

**Class**: Rho kinase inhibitor (first-in-class)
**Approval**: FDA

**Use**: Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

**Benefits**: With once-daily dosing, as effective as twice-daily timolol in reducing intraocular pressure (IOP) in patients with baseline IOP lower than 25mm Hg.

[Prescribing information for Rhopressa®. Revised 12/2017.]

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**Macimorelin acetate** to diagnose growth hormone deficiency

**Product name**: Macrilen®

**Dosage form**: Granules for oral solution

**Class**: Growth hormone (GH) secretagogue receptor agonist; ATC code: V04CD06

**Approval**: FDA

**Use**: Diagnosis of adult growth hormone deficiency.

**Benefits**: More convenient alternative to the insulin tolerance test.

**Safety information**: Risk of QT interval prolongation, should not be used together with medicines known to prolong QT interval.

[Prescribing information for Macrilen®. Revised 12/2017.]

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**Darvadstrocel** to treat complex perianal fistulas in Crohn’s disease

**Product name**: Alofisel®

**Dosage form**: Suspension for injection

**Class**: Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue; advanced therapy medicinal product (ATMP)

**Approval**: EMA (orphan designation)

**Use**: Treatment of complex perianal fistulas in adult patients with Crohn’s disease

**Benefits**: Clinically meaningful ability to improve the healing process of complex perianal fistulas.

[EMA Press release, 15 December 2017.]

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**Voretigene neparvovec for a rare form of inherited vision loss**

**Non-proprietary name in the U.S.**: voretigene neparvovec-rzyl

**Product name**: Luxturna®

**Dosage form**: Intraocular suspension for subretinal injection

**Class**: Adeno-associated virus vector-based gene therapy

**Approval**: FDA (priority review, breakthrough therapy; orphan drug designation)

**Use**: Treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy, a rare inherited condition that leads to vision loss and may cause complete blindness in certain patients. Patients must have viable retinal cells as determined by the treating physician(s).

**Benefits**: Ability to deliver the normal human RPE65 gene to the retinal cells to restore vision.

**Note**: Analysts expect the marketing authorization holder to announce a price approaching and perhaps exceeding $1 million per person. A U.S.-based non-profit organization has called for the company to disclose its research and development costs for this medicine so that analysts, payers and the public have a basis to assess the company’s pricing decision.(1)

[EMA Press release, 15 December 2017.]


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**Biosimilars**

**Insulin glargine**

**Product name**: Semglee®

**Reference product**: Lantus®

**Approval**: EMA

**Use**: Treatment of diabetes mellitus in adults, adolescents and children aged two years and above.

[EMA/CHMP Summary of opinion, 25 January 2018.]
Approved

**Trastuzumab**
*Product name:* Herzuma®  
*Reference product:* Herceptin®  
*Approval:* EMA  
*Use:* Treatment of breast and gastric cancer  
 ► EMA/CHMP Summary of opinion, 14 December 2018.

**Labelling change**

**Nilotinib** – “treatment holiday” possible for certain patients
*Product name:* Tasigna®  
*Use:* Treatment of chronic myeloid leukaemia (CML)  
*Approval of label change:* FDA (priority review; orphan drug designation)  
*Approved change:* Updates to reflect outcomes of clinical trials showing that certain patients may be eligible to stop treatment after a sustained response. This possibility marks a first in the treatment of CML. If treatment is stopped, patients must be regularly monitored for disease recurrence.  
 ► FDA News release, 22 December 2017.

**Extensions of indications**

**Durvalumab** for certain lung cancers
*Product name:* Imfinzi®  
*Approval:* FDA (priority review, breakthrough therapy)  
*Use:* Treatment of patients with unresectable stage III non-small cell lung cancer and whose cancer has not worsened after treatment with chemotherapy and radiation.  
*Benefits:* Ability to extend progression-free survival period after chemoradiation.  
 ► FDA News release, 16 February 2018.

**Olaparib** for certain types of breast cancer
*Product name:* Lynparza®  
*Approval:* FDA  
*Newly approved use:* Treatment of patients with germline breast cancer susceptibility gene (BRCA)-mutated, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have been previously treated with chemotherapy. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior hormonal therapy or be considered inappropriate for endocrine treatment.  
*Notes:* This is the first poly ADP-ribose polymerase (PARP) inhibitor approved by the FDA to treat breast cancer, and the first approved medicine to treat certain patients with metastatic breast cancer who have a BRCA mutation. The FDA has also expanded the approval of the companion diagnostic BRACAnalysis CDx® to include the detection of BRCA mutations in blood samples from patients with breast cancer.  
 ► FDA News release, 12 January 2018.

**Anakinra** for a rare inflammatory disease
*Product name:* Kineret®  
*Approval:* EMA  
*Newly approved use:* Treatment of Still’s disease in patients aged eight months or older  
*Notes:* Still’s disease is a rare disease causing inflammation of joints, rash and fever in children and adults. In children, Still’s disease (systemic juvenile idiopathic arthritis) is the most severe form of arthritis. Most patients are initially treated with NSAIDs and glucocorticoids – often in high doses – followed by second line treatment with monoclonal antibodies. Anakinra provides an efficient alternative treatment option.  