Final FDA guidance on opioids with abuse-deterrent properties

United States of America – The FDA has issued its final guidance to assist industry in developing opioid drug products with potentially abuse-deterrent properties. The document explains the FDA’s current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties. It makes recommendations about how such studies should be performed and evaluated, and discusses what labelling claims may be approved based on the study results.

This guidance does not address generic opioid products. The FDA is working on draft guidance in this area.

► FDA News release, 1 April 2015.

EMA scientific advice on clinical trials leads to faster approvals

European Union – An EMA analysis of marketing authorization application outcomes between 2008 and 2012 has found that companies that changed their clinical development plans in accordance with EMA recommendations were more likely to be granted a marketing authorization.

EMA, through its Scientific Advice Working Party (SAWP), provides scientific advice to applicants in designing clinical trials that are scientifically sound and generate adequate data for regulatory benefit-risk assessment. The analysis found that two out of three clinical trial designs submitted were inadequate, and that the success rate of applications with inadequate trials was half as high (41%) than that of applications with adequate trial designs (84%) or those changed according to SAWP recommendations (86%). The scientific advice thus leads to stronger applications from industry, and protects patients from participating in clinical trials that are unlikely to lead to the approval of new medicines.

► EMA News, 17 April 2015.

Generics information-sharing pilot extended

European Union – The EMA has informed applicants that the deadline for participation in the information-sharing pilot project for generics has been extended. Companies are encouraged to submit expressions of interest.

The European Medicines Agency (EMA) launched this project in January 2015 for centrally approved products as part of the International Generic Drug Regulators Pilot (IGDRP) programme. The pilot allows EMA to share its assessments of applications for generic medicines in real time with collaborating regulatory agencies in order to facilitate the timely authorization and availability of safe, effective and high quality generic medicines worldwide.

► EMA News, 21 April 2015.

WHO Drug Information 28(1); 2014:3-10.
**TGA reviews its guidance on evaluation of biosimilars**

**Australia** – The Therapeutics Goods Administration (TGA) is reviewing its guidance on evaluation of biosimilars in light of a globally evolving understanding of biotherapeutics. In particular, an interim system for naming of biosimilars has been proposed, given that the WHO draft policy *Biological Qualifier - An INN Proposal*, published in July 2014, has superseded the previous position on which the TGA policy was based. The interim system will use the Australian biological name without a specific biosimilar identifier suffix. For example a biosimilar to the reference product Neupogen filgrastim would be named ‘Tradename’ filgrastim.

► *TGA News*, 20 April 2015.

**Updated risk management plan format in Australia**

**Australia** – The TGA has published its updated guideline on submission of risk management plans (RMPs) by companies, including a template for an Australian-specific Annex to RMPs.

An RMP outlines how safety concerns will be identified and mitigated once a pharmaceutical product is on the market to help ensure that the benefit-risk balance remains favourable. Submission of RMPs has been required in Australia since 2009 for all new chemical entities, as well as for already registered products when there is a major change in the way in which the product is used or if a new safety concern is identified.


**Transparency**

**WHO calls for disclosure of clinical trial results**

**Geneva** – WHO has issued a public statement calling for the disclosure of results from clinical trials for medical products, whatever the result, to help all actors to set priorities for research and development as well as public health interventions. The call for disclosure includes older unreported clinical trials, the results of which may still have an important bearing on scientific research today.

WHO also reaffirms the need for all clinical trials to be registered on a WHO primary clinical trial registry so that they can be accessible through the International Clinical Trials Registry platform. This platform was established in response to a 2005 call by WHO. It regularly imports trial records from major national and regional clinical trial registries.

► *WHO Note for the media*, 14 April 2015.

**Australia adopts new regulator performance framework**

**Australia** – The Australian Government has developed a regulator performance framework comprising six outcomes-based key performance indicators (KPIs). The KPIs are supported by a series of qualitative and quantitative outputs and evidence, as developed in consultation with the TGA Industry Consultative Committee and the Australian Therapeutic Goods Advisory Council, to assess the TGA's achievements in the different areas of good regulatory performance.

Databases

Health Canada launches searchable inspection database
Canada – Health Canada has launched its Drug and Health Product Inspections Database, a searchable web tool providing information on foreign and domestic inspections of pharmaceutical manufacturing sites conducted by Health Canada and abroad since 2012. This publicly available database brings together key data about drug establishments and inspection results, including detailed inspections report cards.

The new tool is a milestone under Health Canada’s Regulatory Transparency and Openness Framework. Another useful tool under this framework is Health Canada’s Inspection Tracker, which provides a snapshot of emerging issues identified through the inspection programme and the actions that the authority is taking.

► Health Canada News release, 13 April 2015.

WHO launches open access to its global medicines safety database
WHO has launched an open access platform to its database of suspected adverse reaction reports maintained by the Uppsala Monitoring Centre in Sweden. The platform, named VigiAccess, is a new web application that will allow anyone to access information on reported cases of adverse events related to over 150 000 medicines and vaccines, with more than ten million cases reported from over 120 countries.

By providing open access to this database, WHO aims to improve patient safety, increase transparency and encourage the reporting of adverse effects from medicinal products. The platform can be accessed at www.vigiaccess.org.

► WHO Essential medicines and health products. Media advisory, 17 April 2015.

EMA to record adverse events from literature in EudraVigilance
European Union – A new service offered by EMA is expected to improve safety monitoring of medicines and simplify pharmacovigilance activities for companies. In accordance with the European Union’s (EU) pharmacovigilance legislation, the Agency will screen medical literature for 400 active substance groups and will enter identified reports of suspected adverse reactions into the the EU adverse drug reaction collection and management system, EudraVigilance.

A list of the substances and scientific journals covered is available on the EMA website. The service will start on 1 July 2015 and will be fully rolled out in September 2015.

This initiative will benefit over 4 000 companies that will no longer need to enter suspected adverse reactions into EudraVigilance for the active substances and literature covered.

**Approved**

### Cholic acid for rare bile acid synthesis disorders

**Product name:** Cholbam®
**Dosage form:** Capsules
**Class:** Bile acid preparation  
**ATC code:** A05AA03
**Approval:** FDA (rare paediatric disease priority review)
**Use:** Treatment of patients with bile acid synthesis disorders due to single enzyme defects, and patients with peroxisomal disorders (including Zellweger spectrum disorders)
**Benefits:** First approved treatment option for patients lacking cholic acid due to rare, genetic metabolic disorders. In children, if these conditions are not treated they will impair growth and can lead to life-threatening liver injury.

► **FDA News release, 17 March 2015.**

### Eluxadoline for irritable bowel disease

**Product name:** Viberzi®
**Dosage form:** Tablets
**Class:** Mu-opioid receptor agonist
**Approval:** FDA
**Use:** Treatment of irritable bowel disease with diarrhoea in adults
**Benefits:** Additional treatment option for irritable bowel disease with diarrhoea

**Safety information:** Eluxadoline can cause spasm in the sphincter of Oddi, which can result in pancreatitis. Eluxadoline should not be used in patients with a history of bile duct obstruction, pancreatitis, severe liver impairment, or severe constipation, nor in patients who drink more than three alcoholic beverages per day.

**Note:** The FDA has also approved an extension of indications for rifaximin (Xifaxan®) to include treatment of irritable bowel disease in adults. Rifaximin, an antibiotic derived from rifampicin, was previously approved as treatment for travellers’ diarrhoea caused by *E. coli* and for reduction of the risk in adult patients of recurring overt hepatic encephalopathy.

► **FDA News release, 27 May 2015.**

### Empagliflozin & metformin for diabetes

**Product name:** Synjardy®
**Dosage form:** Film-coated tablets
**Class:** Fixed-dose combination of oral blood glucose lowering agents
**ATC code:** A10BD20
**Approval:** EMA
**Use:** Treatment of adults with type 2 diabetes mellitus as an adjunct to diet and exercise in patients inadequately controlled on other treatments.
**Benefits:** Clinically relevant improvement in glycaemic control compared with metformin on its own.

► **EMA Summary of opinion, 26 March 2015.**

### Evolocumab to lower cholesterol

**Product name:** Repatha®
**Dosage form:** Solution for injection in a pre-filled syringe or in a pre-filled pen
**Class:** Lipid-lowering agent, monoclonal antibody, PCSK9 protein-blocker (first-in-class treatment)
**ATC code:** C10AX13
**Approval:** EMA
**Use:** Treatment of hypercholesterolaemia or mixed dyslipidaemia in adults, and treatment of homozygous familial hypercholesterolaemia in adults and adolescents. The effect of evolocumab on cardiovascular morbidity and mortality has not yet been determined.
**Benefits:** Reduces serum LDL-cholesterol levels in patients who are unable to control their cholesterol with statins.

**Safety information:** The use of evolocumab may lead to very low cholesterol levels where safety has not yet been established.

► **EMA Press release, 22 May 2015.**
Isavuconazonium sulfate for certain invasive fungal infections

**Product name**: Cressemba®
**Dosage form**: Available in oral and intravenous formulations
**Class**: Azole antifungal agent
**Approval**: FDA (Qualified Infectious Disease Product designation)
**Use**: Treatment of invasive aspergillosis and invasive mucormycosis.
**Benefits**: Treatment option for two rare but serious fungal infections.
**Safety information**: Serious potential side effects include liver problems, infusion reactions and severe allergic and skin reactions.

► [FDA News release, 6 March 2015](#).

Atazanavir & cobicistat for treatment of HIV-1 infection

**Product name**: Evotaz®
**Dosage form**: Fixed-dose combination tablets
**Class**: Antiretroviral
**ATC code**: J05AR15
**Approval**: EMA
**Use**: Treatment of HIV-1 infection in adults without known mutations associated with resistance to atazanavir
**Benefits**: Sustainable virological suppression if given in combination with other antiretrovirals.

► [EMA Summary of opinion, 21 May 2015](#).

Anthrax immunoglobulin (human)

**Product name**: Anthrasil®
**Dosage form**: Solution for intravenous injection
**Class**: Specific immunoglobulin
**Approval**: FDA
**Use**: Treatment of patients with inhalational anthrax in combination with appropriate antibacterial drugs
**Benefits**: The results of studies in research animals provided sufficient evidence that the product is reasonably likely to benefit humans with inhalational anthrax.
**Note**: Inhalational anthrax is a rare disease that can occur after exposure to infected animals or contaminated animal products, or as a result of an intentional release of anthrax spores. The product has been purchased for the U.S. Strategic National Stockpile. Its approval makes it available in an emergency without a prior emergency use authorization from the FDA.

► [FDA News release, 25 March 2015](#).

Dinutuximab to prolong survival in children with high-risk neuroblastoma

**Product name**: Unituxin®
**Dosage form**: Injection
**Class**: Antineoplastic agent, monoclonal antibody; **ATC code**: L01XC16
**Approval**: FDA (priority review and orphan product designation); EMA (orphan designation)
**Use**: In combination with other drugs, first-line therapy for paediatric patients with high-risk neuroblastoma, a type of cancer that most often occurs in young children.
**Benefits**: First specific approved treatment to prolong survival in children with high-risk neuroblastoma
**Safety information**: Dinutuximab irritates nerve cells, causing severe pain that requires treatment with intravenous narcotics. Despite prophylaxis, two thirds of children experience pain and about 40% experience severe pain. The medicine can also cause nerve damage and life-threatening infusion reactions, and has some other serious side effects.

► [FDA News release, 10 March 2015](#).
[EMA Press release, 22 May 2015](#).
Isavuconazonium sulfate for certain invasive fungal infections

**Product name:** Cressemba®
**Dosage form:** Available in oral and intravenous formulations
**Class:** Azole antifungal agent
**Approval:** FDA (Qualified Infectious Disease Product designation)
**Use:** Treatment of invasive aspergillosis and invasive mucormycosis.
**Benefits:** Treatment option for two rare but serious fungal infections.
**Safety information:** Serious potential side effects include liver problems, infusion reactions and severe allergic and skin reactions.

► FDA News release, 6 March 2015.

Atazanavir & cobicistat for treatment of HIV-1 infection

**Product name:** Evotaz®
**Dosage form:** Fixed-dose combination tablets
**Class:** Antiretroviral
  *ATC code:* J05AR15
**Approval:** EMA
**Use:** Treatment of HIV-1 infection in adults without known mutations associated with resistance to atazanavir
**Benefits:** Sustainable virological suppression if given in combination with other antiretrovirals.

► EMA Summary of opinion, 21 May 2015.

Anthrax immunoglobulin (human)

**Product name:** Anthrasil®
**Dosage form:** Solution for intravenous injection
**Class:** Specific immunoglobulin
**Approval:** FDA
**Use:** Treatment of patients with inhalational anthrax in combination with appropriate antibacterial drugs

Benefits: The results of studies in research animals provided sufficient evidence that the product is reasonably likely to benefit humans with inhalational anthrax.

Note: Inhalational anthrax is a rare disease that can occur after exposure to infected animals or contaminated animal products, or as a result of an intentional release of anthrax spores. The product has been purchased for the U.S. Strategic National Stockpile. Its approval makes it available in an emergency without a prior emergency use authorization from the FDA.


Dinutuximab to prolong survival in children with high-risk neuroblastoma

**Product name:** Unituxin®
**Dosage form:** Injection
**Class:** Antineoplastic agent, monoclonal antibody; *ATC code:* L01XC16
**Approval:** FDA (priority review and orphan product designation); EMA (orphan designation)
**Use:** In combination with other drugs, first-line therapy for paediatric patients with high-risk neuroblastoma, a type of cancer that most often occurs in young children.
**Benefits:** First specific approved treatment to prolong survival in children with high-risk neuroblastoma

Safety information: Dinutuximab irritates nerve cells, causing severe pain that requires treatment with intravenous narcotics. Despite prophylaxis, two thirds of children experience pain and about 40% experience severe pain. The medicine can also cause nerve damage and life-threatening infusion reactions, and has some other serious side effects.

► FDA News release, 10 March 2015.
Filgrastim-sndz, first biosimilar in the U.S.

**Placeholder nonproprietary name**: Filgrastim-sndz

**Product name**: Zarxio®

**Dosage form**: Solution for injection or infusion

**Class**: Immunostimulant, colony stimulating factor; **ATC code**: L03AA02

**Reference product**: Filgrastim (Neupogen®)

**Approval**: FDA

**Use**: To reduce the effects of neutropenia in patients with cancer receiving various types of chemotherapy or undergoing bone marrow transplantation and in patients with severe chronic neutropenia; to mobilize blood progenitor cells into the peripheral blood for collection and autologous therapy.

**Benefits**: Reduction of neutropenia

**Note**: This is the first biosimilar product approved in the U.S. through the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), which created an abbreviated regulatory pathway for biosimilars. Biosimilar filgrastim products have been marketed in various countries outside the U.S.

*A comprehensive naming policy for biosimilar and other biological products remains to be adopted. The FDA intends to issue draft guidance in the near future on how current and future biological products marketed in the U.S. should be named.

*EMA Press release, 24 April 2015.*

---

**Extensions of indications**

**Moxifloxacin for treatment of plague**

**Product name**: (Avelox®)

**Dosage form**: Tablets

**Class**: Antibacterial, fluoroquinolone; **ATC code**: J01MA14

**Approval**: FDA

**Newly approved use**: Treatment of pneumonic plague and septicemic plague; prevention of plague in adult patients

**Note**: The approval was granted based on an animal study, as it would not have been feasible or ethical to conduct trials in humans.

*FDA News Release, 8 May 2015.*

**Sirolimus for very rare lung disease**

**Product name**: Rapamune®

**Dosage forms**: Tablet, oral solution

**Class**: Selective immunosuppressant; **ATC code**: L04AA10

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

**Newly approved use**: Treatment of lymphangioleiomyomatosis (LAM), a rare, progressive lung disease that primarily affects women of childbearing age.

**Safety information**: Serious side effects including hypersensitivity and swelling (edema) have been observed in renal transplant patients.

**Note**: This is the first medicine approved in the U.S. to treat LAM.

*FDA News release, 28 May 2015.*

---

**Tasimelteon to regulate sleep patterns in blind adults**

**Product name**: Hetlioz®

**Dosage form**: Hard capsules

**Class**: Psycholeptic, melatonin receptor agonist; **ATC code**: N05CH03

**Approval**: EMA (orphan designation)

**Use**: Treatment of non-24-hour sleep-wake disorder in totally blind adults.

**Benefits**: Ability to entrain the master body clock in people who do not perceive light, and whose sleep-wake pattern is not synchronized with the 24-hour clock.

*FDA News release, 6 March 2015.*

---

**Approved**
Generic

**Glatiramer acetate**
A complex active ingredient
Reference product: Copaxone®
Dosage form: Injection
Class: Immunostimulant; *ATC code*: L03AX13
Approval: FDA
Use: Treatment of relapsing forms of multiple sclerosis
Note: The reference product is a copolymer mixture with inherent batch-to-batch variability. For this approval, FDA scientists therefore established a scientific approach for demonstrating that the active ingredient of the generic is the same as that of the reference product.

► *FDA News release, 16 April 2015.*

Early access

**Pembrolizumab**
Early access in the United Kingdom
Product name: Keytruda®
Dosage form: Powder for concentrate for solution for infusion
Class: Antineoplastic; monoclonal PD-1 antibody. *ATC code* (temporary): L01XC18

Approval: EMA (previously approved in the U.S. in September 2014)
Use: Treatment of unresectable or metastatic melanoma
Benefits: Can slow the progression of cancer in a condition where other treatments currently have poor results.
Safety information: Pembrolizumab may be associated with side effects resulting from excessive activity of the immune system. Most will resolve following appropriate treatment or on stopping pembrolizumab.
Note: Pembrolizumab is the first medicine to be approved in the United Kingdom under the MHRA’s Early Access to Medicines Scheme (EAMS), ahead of receiving a positive recommendation from EMA. The EAMS was introduced in 2014 to provide early access to new medicines in the United Kingdom for patients that have a high unmet clinical need. The scientific opinions issued under this Scheme describe the risks and benefits of the medicine and the context for its use, supporting the prescriber and the patient to make a decision on whether to use the medicine before its licence is approved.

► *MHRA Announcement, 11 March 2015.*