Regulatory news

**Pre-market assessment**

**Generics information-sharing pilot expanded**

**European Union** – The EMA is ready to share its assessments of applications also for generic medicines that fall under the EMA’s centralized procedure. The information-sharing initiative started in July 2014 using the EU decentralized procedure as a model.

This initiative, under which EU assessment information is shared in real time with collaborating regulatory agencies outside the European Union (EU), is part of the International Generic Drug Regulators Pilot (IGDRP). It brings together 14 regulatory authorities as well as the European Directorate for the Quality of Medicines & Healthcare (EDQM) and WHO as observers.

The first phase of the pilot project will involve the EU, Australia, Canada, Chinese Taipei and Switzerland. Ten applications for generic medicines will be selected initially. Further information has been published on the EMA website.

► EMA news, 19 January 2015.

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

**Pharmacovigilance**

**EMA upgrades data systems**

**European Union** – The EMA has completed two separate steps to develop its reporting systems in accordance with the EU pharmacovigilance legislation.

Firstly, the Agency has published a guide to support the implementation of a new international ISO standard for reporting of suspected side effects of medicines in Individual Case Safety Reports (ICSRs). The standard will enhance the European EudraVigilance adverse events database. It will bring a globally harmonized format for case reports collected by pharmaceutical companies and regulatory authorities, better quality of data to detect and address medicines safety issues, and stronger personal data protection. The use of the new standard will take effect on 1 July 2016. (1)

Secondly, the EMA has launched a centralized electronic repository for periodic safety update reports (PSURs) and their assessment reports. The platform will make it easier for regulators...
to access the information and for industry to submit their PSURs electronically. (2)  
► (1) EMA News, 21 January 2015.  
(2) EMA News, 26 January 2015.

Canada launches drug safety information web site  
Canada – The Government of Canada has launched a new online tool for drug safety information. The Drug and Health Product Register provides consumers with centralized access to information on prescription drugs, including their indications, safety warnings and precautions, common side effects, and adverse reactions that have been reported to Health Canada.

Currently in its pilot phase, the Drug and Health Product Register covers the top 100 prescribed products based on IMS-reported Canadian sales for 2013, together with an additional 250 products that have the same active ingredient(s).

The Drug and Health Product Register is one of several initiatives undertaken as part of Canada’s Regulatory Transparency and Openness Framework.  

FDA proposes new guidance on compounding  
United States of America – The FDA has released for comment five draft documents related to compounding of human drugs. The documents include draft guidance texts on registering an outsourcing facility; adverse event reporting by outsourcing facilities; repackaging of drugs; mixing, diluting and repackaging of biological products; and a draft Memorandum of Understanding between the FDA and the states.

The draft documents are applicable to pharmacies, federal facilities, outsourcing facilities and physicians. The new category of outsourcing facilities was created in 2013 in response to a fungal meningitis outbreak that was linked to contaminated compounded drug products.  
► FDA News release, 13 February 2015.

CFDA strengthens good practice guidance for medical devices  
China – The China Food and Drug Administration (CFDA) has issued two regulatory good practice documents for medical devices: the revised Good Manufacturing Practice for Medical Devices, effective from 1 March 2015 (1), and the country’s first Good Supply Practices for Medical Devices, effective from 12 December 2014 (2).

The two guidance texts are part of strengthened regulation for medical devices, including in vitro diagnostic products, in line with current international regulatory principles.  
► (1) CFDA Press release, 19 January 2015.  
(2) CFDA Press Release, 20 January 2015.

Antibiotics  
EMA advice on antibiotics use in animals  
European Union – The EMA has published recommendations to minimize antimicrobial resistance arising from the use of antibiotics in veterinary medicines, especially those that are critically important in human medicine, such as fluoroquinolones and third and fourth generation cephalosporins.
Measures are proposed to identify public health risks early in the product life cycle, to monitor antibiotics use and emerging resistance, and to restrict antibiotic use in animals in case of significant public health risks. Tools are also proposed to ban or limit the off-label use in animals of certain antimicrobials authorized only in human medicine.

The advice will serve as input into the discussions that have now started in the European Council and the European Parliament on revising the legislation on veterinary medicines.


**ECDC/EFSA/EMA first joint report**

European Union – The European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) have published their first integrated data analysis on antimicrobial resistance in bacteria from humans and food-producing animals. The report combines data from five monitoring networks that gather information from EU Member States, Iceland, Norway and Switzerland.

In both humans and animals, the analysis found positive associations between consumption of antimicrobials and the corresponding resistance in bacteria for most of the combinations investigated. Despite data limitations, these findings highlight the need to promote the responsible use of antimicrobials in both humans and animals. The report will inform the European Commission’s action plan against the rising threats from antimicrobial resistance.

► EMA Press release, 30 January 2015.

**Drug availability**

**Canada announces requirement for reporting of drug shortages**

Canada – The Government of Canada is moving towards a mandatory reporting system that will require manufacturers to publicly report actual and anticipated drug shortages. Drug shortages are a complex global problem that can have devastating consequences for certain patients. An advanced warning of upcoming shortages will enable Canadians to proactively work with their healthcare professionals to find alternative treatment options.

While regulations as well as a new, independent third-party website for this reporting are being developed, manufacturers are expected to voluntarily post information on all shortages on the industry-run website [www.drugshortages.ca](http://www.drugshortages.ca), which was launched in March 2012.


**EU industry proposal on reducing manufacturing-related medicines shortages**

European Union – The pharmaceutical industry, through its associations, has proposed a collaborative contribution to help reduce drug shortages caused by manufacturing, quality and/or GMP issues, a subset of the many diverse root causes for shortages. The proposal encompasses communication principles as well as prevention plans both at system level and at product level (1).

The proposal was made in response to a 2012 EMA Reflection paper on medicinal product supply shortages caused by manufacturing issues (2). Despite existing reporting requirements in the EU and the U.S., drug shortages remain a global challenge. In recent years,
Bupropion & naltrexone for weight management

Product name:
EU: Mysimba®; U.S.: Contrave®
Dosage form: Prolonged release tablet
Class: Combination of an antidepressant and a drug used in dependence disorders;
ATC code (temporary classification): A08AA62
Approval: EMA, FDA
Use: Weight management of obese adults or overweight adults having certain risk factors, in addition to a reduced-calorie diet and physical activity (prescription-only).
Benefits: Additional option to help manage the weight-related risks for chronic diseases such as diabetes and cardiovascular disease.
Safety information: Safety and tolerability issues have been identified relating to central nervous system and gastrointestinal adverse events, as well as uncertainties about cardiovascular outcomes in the longer term. Both EMA and FDA require some post-marketing monitoring and/or risk management measures for this product.

Liraglutide for weight management

Product name: Saxenda®
Dosage form: Once-daily injection in a pre-filled pen
Class: Glucagon-like peptide-1 (GLP-1) receptor agonist
ATC code: A10BX07
Approval: FDA, EMA
Use: Weight management, in combination with a reduced-calorie diet and physical activity, in obese adults or overweight adults with at least one weight-related health condition (prescription-only).
Benefits: Additional treatment option for chronic weight management to mitigate the risk of chronic health conditions.
Safety information: Some serious side effects have been reported in patients treated with GLP-1-based therapies, including an increased heart rate, pancreatitis, gallbladder disease, renal impairment and suicidal thoughts. In the U.S. the product also has a boxed warning against use in patients with a personal or family history of medullary thyroid carcinoma (MTC) or those with multiple endocrine neoplasia syndrome type 2, which predisposes them to MTC. Both EMA and FDA require some post-marketing monitoring and/or risk management measures for this product.

Note: Concerns have been voiced about the safety of this product, considering its potential adverse effects and past regulatory decisions on other weight management products in the EU.

> FDA News release, 10 September 2014.

Notes: Liraglutide is already approved in the U.S. and the EU at a lower dose for the treatment of diabetes under the trade name Victoza®.
**Cangrelor anti-clotting agent**  
**Product name:** Kengrexal®  
**Dosage form:** Powder for concentrate for solution for infusion  
**Class:** Platelet aggregation inhibitor  
**ATC code:** B01AC25  
**Approval:** EMA  
**Use:** Co-administered with acetylsalicylic acid ASA, to reduce thrombotic cardiovascular events in adult patients with coronary artery disease undergoing percutaneous coronary intervention.  
**Benefits:** Ability to prevent thrombotic cardiovascular events in patients who have not received oral P2Y12 inhibitors before percutaneous coronary intervention.  
► EMA/CHMP Opinion, 22 January 2015.

**Edoxaban anti-clotting agent**  
**Product name:** Savaysa®  
**Dosage form:** Tablets  
**Class:** Anticoagulant; direct Factor Xa inhibitor  
**Approval:** FDA  
**Use:** To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation that is not caused by a heart valve problem, and to treat deep vein thrombosis and pulmonary embolism in patients already treated with a parenteral anticoagulant for five to ten days.  
**Benefits:** Similar efficacy and a lower risk of major bleeding, compared with warfarin.  
**Safety information:** Bleeding is the most serious risk with edoxaban; no treatment has been proven to reverse its anticoagulant effect. The medicine carries a Boxed Warning on dosing and safety in specific patient groups, including a warning that an alternative anti-clotting agent should be used in atrial fibrillation patients with a creatinine clearance > 95 ml/min (>1.58 ml/s).  
► FDA News release, 8 January 2015.

**Tolvaptan for rare kidney disease**  
**Product name:** Jinarc®  
**Dosage form:** Tablets  
**Class:** Vasopressin-2-receptor antagonist  
**ATC code:** C03XA01  
**Approval:** EMA (orphan designation)  
**Use:** Treatment of autosomal dominant polycystic kidney disease (ADPKD) in patients with normal to moderately reduced kidney function who have rapidly progressing ADPKD.  
**Benefits:** Ability to slow the progression of cyst growth and renal insufficiency in adult patients with ADPKD  
**Safety information:** A pharmacovigilance plan will be implemented with additional monitoring of the risk of liver damage.  
**Notes:** This is the first medicine approved in the EU specifically for the treatment of ADPKD. Tolvaptan is already authorized in the EU under the trade name Samsca® for treating hyponatraemia, although the doses studied in ADPKD are different.  

**Parathyroid hormone to control blood calcium levels in hypoparathyroidism**  
**Product name:** Natpara®  
**Dosage form:** Once-daily injection  
**Class:** Parathyroid hormone  
**ATC code:** H05AA03  
**Approval:** FDA (orphan drug designation)  
**Use:** Regulation of blood calcium levels in patients with hypoparathyroidism  
**Benefits:** Alternative treatment option for patients whose calcium levels cannot be controlled on calcium supplementation and active forms of vitamin D.  
**Safety information:** Potential risk of osteosarcoma according to studies in rats. Only available through a restricted programme under a Risk Evaluation and Mitigation Strategy (REMS).  
► FDA News release, 23 January 2015.
Approvals

Ceftolozane & tazobactam for certain complicated infections
Product name: Zerbaxa®
Dosage form: Powder for intravenous infusion
Class: Combination of a cephalosporin antibacterial (ceftolozane) and a beta-lactamase inhibitor (tazobactam);
ATC code (temporary classification): J01DI54
Approval: FDA, Qualified Infectious Disease Product (QIDP) designation
Use: Treatment of adults with complicated intra-abdominal infections and complicated urinary tract infections
Benefits: New treatment option for certain types of serious or life-threatening infections.
Safety information: The product label includes a warning about decreased efficacy seen in patients with renal impairment.

Ceftazidime & avibactam for certain complicated infections
Product name: Avycaz®
Class: Combination of a previously approved cephalosporin antibacterial (ceftazidime), and a new beta-lactamase inhibitor (avibactam).
Approval: FDA (priority review, Qualified Infectious Disease Product, QIDP)
Use: Treatment of complicated intra-abdominal infections in combination with metronidazole, and of complicated urinary tract infections including pyelonephritis, in adult patients who have limited or no alternative treatment options.
Benefits: Treatment option when there are limited or no alternative antibacterial drugs for treating a patient’s infection. Use of this product is reserved to such situations.
Safety information: Risk of rare but serious skin or hypersensitivity reactions such as Stevens-Johnson syndrome and erythema multiforme. Patients with influenza may be at an increased risk of hallucinations, delirium and abnormal behaviour early in their illness and should be monitored.
Note: This is the first FDA-approved neuraminidase inhibitor for intravenous administration.
► FDA News release, 22 December 2014.

Finafloxacin for outer ear infection
Product name: Xtoro®
Dosage form: Otic suspension
Class: Fluoroquinolone
Approval: FDA
Use: Treatment of acute outer ear infection caused by Pseudomonas aeruginosa and Staphylococcus aureus.
Benefits: New antibacterial medicine with proven efficacy for the target conditions.

Peramivir for influenza
Product name: Rapivab®
Dosage form: Single-dose intravenous injection
Class: Neuraminidase inhibitor
Approval: FDA
Use: Treatment of uncomplicated influenza in adults who have had symptoms of influenza for no more than two days.
Benefits: Single-dose intravenous treatment option for uncomplicated influenza.
Safety information: Risk of rare but serious skin or hypersensitivity reactions such as Stevens-Johnson syndrome and erythema multiforme. Patients with influenza may be at an increased risk of hallucinations, delirium and abnormal behaviour early in their illness and should be monitored.
Note: This is the first FDA-approved neuraminidase inhibitor for intravenous administration.
► FDA News release, 22 December 2014.

Lamivudine & raltegravir
Product name: Dutrebis®
Dosage form: Film-coated tablets
Class: Antivirals for HIV infection
ATC code: J05AR16
Approval: EMA
Use: Treatment of HIV infection
Benefits: Improved dosing regimen with a reduced daily pill burden.
► EMA/CHMP Opinion, 22 January 2015.
**Meningococcal serogroup B vaccine**  
*Product name:* Bexsero®  
*Dosage form:* Suspension for injection in a pre-filled syringe  
*Class:* Meningococcal serogroup B vaccine  
*ATC code:* J07AH09  
*Approval:* FDA (accelerated approval; breakthrough therapy)  
*Use:* Prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B in individuals 10 through 25 years of age.  
*Notes:* Bexsero® is the second licensed meningococcal group B vaccine in the U.S., after Trumenba® licensed in October 2014.  
► *FDA News release, 23 January 2015.*

**Human Papillomavirus 9-valent Vaccine, Recombinant for prevention of certain cancers**  
*Product name:* Gardasil 9®  
*Dosage form:* Suspension for intramuscular injection  
*Class:* Human Papillomavirus 9-valent Vaccine, Recombinant  
*Approval:* FDA  
*Use:* Prevention of certain diseases caused by nine types of Human Papillomavirus (HPV)  
*Benefits:* Added protection against five additional HPV types—31, 33, 45, 52 and 58—which cause approximately 20 percent of cervical cancers and are not covered by previously FDA-approved HPV vaccines.  
► *FDA News release, 10 December 2014.*

**Sabin inactivated polio vaccine (sIPV)**  
*Product name:* Ai Bi Wei (brand name in China)  
*Dosage form:* Injection  
*Class:* Inactivated poliomyelitis vaccine (IPV), Sabin strain  
*Approval:* China Food and Drug Administration (CFDA)  
*Use:* Vaccination against poliomyelitis  
*Benefits:* This vaccine will play a critical role for the eradication of poliomyelitis in China. (1)  
*Note:* This is the second Sabin IPV to be licensed worldwide. The Global Polio Eradication Initiative’s Eradication and Endgame Strategic Plan 2013–18 calls for IPV to be introduced into immunization programmes. The CFDA-approved IPV vaccine could play an important role in global polio eradication if it is shown to meet international quality standards. In October 2013 the first produced in China—a vaccine against Japanese encephalitis—achieved WHO prequalification, making it acceptable for procurement by international organizations such as UNICEF and the GAVI Alliance. (2)  
► (1) *CFDA Press release, 16 January 2015.*  

**Ceritinib for certain lung cancers**  
*Product name:* Zykadia®  
*Dosage form:* Hard capsule  
*ATC code:* L01XE28  
*Class:* Protein kinase inhibitor  
*Approval:* EMA (conditional marketing authorization – requirement for further results from ongoing studies and a comparative phase III study within the next three years)  
*Use:* Treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer previously treated with crizotinib  
*Benefits:* Treatment option for a high unmet medical need in patients previously treated with crizotinib, as treatment options are currently very limited.  
*Safety information:* The most serious adverse reactions are hepatotoxicity,
gastrointestinal effects, QT interval prolongation, bradycardia, interstitial lung disease/pneumonitis and hyperglycaemia.


**Nivolumab for advanced melanoma and lung cancer**

**Product name:** Opdivo®

**Dosage form:** Injection solution for intravenous infusion

**Class:** Monoclonal antibody, PD-1 blocker

**ATC Code (temporary classification):** L01XC17

**Approval:** FDA (breakthrough therapy, priority review and orphan product designations)

**Use:** Treatment of unresectable or metastatic melanoma that no longer responds to other medicines. (1)

**Benefits:** Additional treatment option for patients previously treated with ipilimumab and – in the case of patients whose tumours express a BRAF V600 mutation – a BRAF inhibitor.

**Subsequently approved use:** Treatment of advanced (metastatic) squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy. (2)

**Safety information:** The most serious adverse effects are severe immune-mediated side effects involving healthy organs, including the lung, colon, liver, kidneys and hormone-producing glands.

► (1) FDA News release, 22 December 2014.

(2) FDA News release, 4 March 2015.

**Palbociclib for advanced breast cancer**

**Product name:** Ibrance®

**Dosage form:** Capsules

**Class:** Antineoplastic agent; cyclin-dependent kinase (CDKs) 4 and 6 inhibitor

**Approval:** FDA (accelerated approval, breakthrough therapy)

**Use:** Treatment of certain metastatic breast cancers in postmenopausal women who have not yet received an endocrine-based therapy. Palboclicib is to be used in combination with letrozole (Femara®)

**Benefits:** New treatment option for certain types of metastatic breast cancer.

► FDA News release, 3 February 2015.

**Safinamide for Parkinson’s disease**

**Product name:** Xadago®

**Dosage form:** Film-coated tablets

**Class:** Selective and reversible monoamine oxidase B (MAO-B) inhibitor

**Approval:** EMA

**Use:** Treatment of adult patients with idiopathic Parkinson’s disease as add-on therapy
Benefits: Ability to prolong the times during which symptoms are adequately controlled (“on” times) in patients with motor fluctuations receiving L-dopa alone or in combination with other medications for Parkinson’s disease.


Autologous limbal stem cells for limbal stem cell deficiency due to burns to the eyes

Product name: Holoclar®
Living tissue equivalent intended to be transplanted in the affected eye(s), made from a biopsy taken from the patient’s cornea and grown in cell culture.

Class: Ex-vivo expanded autologous human corneal epithelial cells containing stem cells, ophthalmological product
ATC code: S01XA19
Approval: EMA (orphan designation)
Use: Treatment of moderate to severe limbal stem cell deficiency due to physical or chemical burns to the eye(s) in adults.
Benefits: Ability to repair the damaged ocular surface, to improve or resolve symptoms of pain, photophobia and burning, and to improve the patient’s visual acuity.
Note: This is the first stem-cell therapy recommended for approval in the EU.

Extensions of indications


<table>
<thead>
<tr>
<th>Product</th>
<th>Newly approved indication</th>
<th>Reviewing authority reference</th>
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<tbody>
<tr>
<td>Lenalidomide</td>
<td>Continuous treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.</td>
<td>► EMA/CHMP Opinion, 18 December 2014.</td>
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<tr>
<td>(Revlimid®) Hard capsule</td>
<td></td>
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<tr>
<td>Bevacizumab</td>
<td>In combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix.</td>
<td>► EMA/CHMP Opinion, 26 February 2015.</td>
</tr>
<tr>
<td>(Avastin®) Concentrate for solution for intravenous infusion</td>
<td></td>
<td></td>
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<tr>
<td>Paclitaxel</td>
<td>In combination with carboplatin, first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.</td>
<td>► EMA/CHMP Opinion, 22 January 2015.</td>
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<tr>
<td>(Abraxane®) Powder for suspension for infusion</td>
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### Extensions of indications

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<tr>
<td><strong>Ibrutinib</strong> <em>(Imbruvica®)</em>&lt;br&gt;Capsules</td>
<td>Treatment of Waldenström’s macroglobulinaemia, a rare form of cancer that begins in the body’s immune system. Note: This is the first drug approved worldwide specifically for treatment of Waldenström’s macroglobulinaemia.</td>
<td>FDA (breakthrough therapy, priority review, and orphan product designation)►FDA News release, 29 January 2015.</td>
</tr>
<tr>
<td><strong>Bortezomib</strong> <em>(Velcade®)</em>&lt;br&gt;Powder for solution for injection</td>
<td>In combination with rituximab, cyclophosphamide, doxorubicin and prednisone treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.</td>
<td>EMA/CHMP Opinion, 18 December 2014.</td>
</tr>
<tr>
<td><strong>Lisdexamfetamine</strong>&lt;br&gt;dimesylate <em>(Vyvanse®)</em>&lt;br&gt;Capsules</td>
<td>Treatment of binge eating disorders in adults - first FDA-approved medication to treat this condition. Safety information: The most serious risks include psychiatric problems and heart complications. Lisdexamfetamine is a Schedule II controlled substance in the U.S. because of its high potential for abuse.</td>
<td>FDA (priority review)►FDA News release, 30 January 2015.</td>
</tr>
<tr>
<td><strong>Ranibizumab</strong> <em>(Lucentis®)</em>&lt;br&gt;Injection</td>
<td>Treatment of diabetic retinopathy in patients with diabetic macular oedema. The drug is intended to be used together with appropriate interventions to control blood sugar, blood pressure and cholesterol. Safety information: Endophthalmitis and retinal detachments are the two most serious side effects associated with ranibizumab.</td>
<td>FDA (breakthrough therapy designation, priority review)►FDA News Release, 6 February 2015.</td>
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<tr>
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<tbody>
<tr>
<td><strong>Palonosetron</strong></td>
<td>Prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy, and prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in paediatric patients 1 month of age and older.</td>
<td>► EMA/CHMP Opinion, 22 January 2015.</td>
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Labelling changes

**Diabetes pen devices for single-patient use only**

*Product*: Multi-dose diabetes pen devices  
*Regulatory authority*: FDA  
*Labelling change*: The FDA requires that pens and packaging containing multiple doses of insulin and other injectable diabetes medicines display a warning label stating “For single patient use only.” Additional warnings against sharing pens will also be added to the prescribing information and to the patient Medication Guides, Patient Package Inserts, and Instructions for Use.  
*Note*: Even if the needle is changed insulin pens and pens for other injectable diabetes medicines should never be shared among patients, as blood may be present in the pen after use. The requirement was introduced to reduce the serious risk of infection spread through sharing of multi-dose diabetes pen devices.  

**Xpert® MTB/RIF test can guide decisions on ending patient isolation**

*Product name*: Xpert® MTB/RIF Assay  
*Test type*: Nucleic acid amplification test to detect *M. tuberculosis* complex and genetic markers for rifampicin resistance.  
*Regulatory authority*: FDA  
*Labelling change*: Revised labelling states that the results from one or two consecutive negative MTB/RIF tests strongly predict the results that would be obtained from acid-fast bacilli smear testing of three sputum specimens collected eight to 24 hours apart. Results from one or two MTB/RIF tests (depending on the specific patient being tested and hospital guidelines) can be used in the decision to remove patients from airborne infection isolation.  
*Caution*: The MTB/RIF test may not detect all patients with active tuberculosis (TB). The FDA advises that healthcare workers should also continue to follow current CDC guidelines to collect consecutive sputum specimens for TB culture testing, even if results from MTB/RIF testing are negative.  