WHO Drug Information

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Quality and Safety of Medicines

WHO project for the surveillance and monitoring of SSFFC medical products

The existence of substandard/spurious/falsely labelled/falsified and counterfeit (SSFFC) medical products is not a new phenomenon, but is increasingly recognized by WHO Member States, regional groups and various international organizations as representing a significant threat to human health.

The right to safe, efficacious, quality medicines which are affordable is a fundamental human right. In some low income countries access to healthcare facilities is limited; for those fortunate enough to reach a facility they should be able to have trust and confidence in the medicines they receive. Often, this is not the case and with tragic consequences. However, this situation — which was once regarded as an issue solely affecting low and middle income countries — now impacts all. The vast profits to be made through the high demand and large turnover of medical products is a powerful driver for those engaged in the manufacture, distribution and supply of SSFFC medical products.

The rapid increase in connectivity to the Internet has also effectively opened up global markets to the distribution of SSFFC medical products. Whilst enabling access to medicines, it has also encouraged a culture of self-diagnosis and self-prescribing. Unregulated websites have been seen in some parts of the world as a key source of SSFFC products: an issue which is impossible to regulate effectively and cannot be dealt with by one country in isolation.

Worryingly, incidents involving SSFFC products are frequently reported from hospitals, clinics, pharmacies and licensed entities within the regulated supply chain — precisely the places where patients should have the highest level of confidence that the medicines they receive are safe and effective. Every incident damages confidence in health systems, medicines and healthcare professionals.

Despite this situation, there is no accurate global assessment of the scope, scale and harm caused by the issue. Much anecdotal information exists, but there is a lack of clear, validated, reliable evidence. Some excellent surveys have been conducted in various parts of the world. However, these reports are often short-term, restricted to limited geographic areas and may concentrate on specific therapeutic categories. They are frequently used to extrapolate an estimate of the global threat which is less than sound and commonly challenged. Policy makers require reliable evidence upon which to base sound decisions concerning the allocation of finite resources to tackle this damaging issue in a proportionate way.

Surveillance and monitoring

In 2010, WHO began to re-examine existing methods and systems of collecting data concerning SSFFC medical products. A rapid alert system had been developed in the Western Pacific Region but was not being regularly used. During 2011, two consultative meetings were held in Kiev, Ukraine and Kuala Lumpur, Malaysia. National regulatory authorities from the respective regions were asked to participate and
agree on methods to encourage the reporting of incidents.

Building upon the good work started in the Western Pacific Region, a new surveillance and monitoring system was designed utilizing the submission of a clear, concise and structured Rapid Alert Form to encourage a more systematic method of reporting. The objective of the project is to significantly improve the quantity and quality of data enabling detailed analysis and validation of incidents.

**Rapid Alert Form**

Following further consultation, an electronic Rapid Alert Form was designed. This template contains what is considered to be the minimum amount of information for WHO to conduct an initial risk assessment. Some of the data fields are mandatory and failure to complete these fields will prevent the document from being forwarded to WHO.

The Rapid Alert Form contains a hidden language recognition code. This enables the form to be completed in one language and automatically translated to English when downloaded into a data base retained at WHO Headquarters. The Rapid Alert Form is currently available in English and a French Version is being tested. It is planned to make Spanish, Russian, Arabic and Mandarin versions available.

The form is provided as a template to trained focal points within national regulatory agencies. Once the mandatory fields are completed, the document can be saved and sent as an attachment via e-mail to rapidalert@who.int. Focal points are encouraged to send any photographs, laboratory reports or other relevant documents as attachments.

Once sent, the originator will receive an automated message confirming receipt and notifying them that they will be contacted by WHO within 72 hours. (In cases where adverse reactions are reported this is 24 hours).

**SSFFC data base**

On arrival at WHO, the details contained on the Rapid Alert Form are automatically downloaded and will populate the SSFFC data base. The system will immediately identify duplicate reports. For example, it will recognize if the specific batch/lot number of a medical product has been previously reported and will also match a range of other details. This allows cross matching of incidents and enables WHO to put Member States in contact with each other if dealing with linked incidents.

At WHO, staff within the Quality and Safety of Medicines Team will also receive automatic notification of the arrival of a rapid alert. They will conduct an immediate risk assessment with a focus on the current threat to public health and the need to communicate the incident to any other countries which may be affected. Sharing of information is only conducted following consultation with the originator of the report.

**Review and analysis**

WHO staff will make contact with the originator of the Rapid Alert either by telephone or e-mail and ask some additional questions. They will start to populate the data base manually with any further information obtained from the originator. The data base contains over 250 fields which can be cross searched in any combination, permitting detailed analysis. The areas explored in more detail contained within the data base include: suspect product details, laboratory analysis, impact on public health, risk communication, dissemination, method of distribution, method of discovery, means and route of import or export, details of who is responsible for any investigation, details of internet distribution, cost of medical product, photographs of product and free text comment and analysis areas.
During this process, an analyst will be looking for a range of characteristics in order to make a final classification of the case. Those characteristics include;

- Unauthorized attempt to visually imitate the licensed, authorized or approved product.
- Attempt to mislead any person concerning product ingredients.
- Incorrect, misleading or missing information as to the place of origin or manufacture.
- Falsification of safety or security features.
- Falsification of batch number, date of manufacture or expiry dates.
- Falsification of any other aspect of packaging.
- Falsification of license status, registration, authorisation or approval information on packaging.
- Falsification of accompanying documentation.
- Was the product concealed or misdeclared during shipment?
- Was the product stolen or diverted?

**Final classification**

Most cases should be closed within 90 days and classified. The final classification is designed to separate substandard medicines caused by genuine manufacturing error from incidents that demonstrate a clear intention to deceive a patient, consumer, healthcare professional, or anybody else that the product is the genuine article.

This final classification ensures that future trend analysis is based upon the comparison of similar incidents. Reports sometimes suggest that a product is falsified when in fact it is substandard due to an honest manufacturing error. It is only after validation has been sought from the originator that a final classification can be carried out.

**Training workshop and pilot study**

Following the consultation process, ten Member States agreed to participate in a pilot study. They are: Cambodia, Croatia, Georgia, Indonesia, Kyrgyzstan, Malaysia, Philippines, Russia, Ukraine, Viet Nam.

In September 2012, the first 3-day SSFFC training workshop was hosted in Manila by the Philippines Food and Drug Administration and held at the WHO Regional Office. The focal points from the ten pilot countries together with their immediate managers attended and participated in five exercises involving recent SSFFC incidents. The USA and China sent observers from their respective regulatory agencies who fully participated in the workshop. At the conclusion of each exercise, delegates were required to complete and submit the Rapid Alert Form to WHO. This training was immediately followed by the pilot study.

This took place between September 2012 and January 2013. Forty reports involving 72 medical products were reported during this period concerning 30 active pharmaceutical ingredients. The pilot study was designed to thoroughly test the system and identify scope for improvement. A number of refinements were made to both the Rapid Alert Form, to improve ease of completion, and the data base, to facilitate better analysis.

**Challenges**

Incidents involving SSFFC medical products are hard to detect. It can be difficult to identify the harm caused by the SSFFC product in a patient who is already suffering from a disease. However, WHO is working closely with the WHO Collaborating Centre in Uppsala to develop methods for mining data
Case Study

In May 2013, WHO issued a drug alert relating to an antimalarial medicine circulating in Western and Central Africa which contained no active pharmaceutical ingredient. This branded product is a WHO prequalified medicine and was being distributed as part of the Global Fund AMFm programme. The genuine product is a reliable, trusted and effective medicine sought after in many sub-Saharan countries as an effective treatment for malaria. A German nongovernmental organization reported to WHO that samples they had recovered in Cameroon had failed mini-lab screening and had been sent to a WHO prequalified laboratory in Kenya for further analysis. Testing confirmed that the sample contained no active pharmaceutical ingredient. Further investigation with the genuine manufacturer of the medicine revealed that the same medicine bearing the same batch number had been seized in Angola as part of a World Customs Organization operation. A second batch of the same medicine had also been recovered during market surveillance in Benin and Nigeria. Recent information also suggested that at least two falsified batches containing no active pharmaceutical ingredient were currently circulating in Western and Central Africa. Initially, WHO issued a warning to all national regulatory authorities requesting increased vigilance. WHO was satisfied that a current and credible risk had been clearly identified which led to the publication of a WHO international drug alert to all Member States and publication on the WHO website.

Next Steps

WHO is confident that a robust and reliable system is now in place to receive reports on incidents suspected to involve SSFFC medical products. Three further training workshops are planned for 2013 in Nigeria, Tanzania and Tunisia, which will bring regulatory, pharmacovigilance and laboratory experts together.

Since the conclusion of the pilot study, reports have continued to be submitted to WHO from a number of different sources. Over 130 products have now been reported and are undergoing review and analysis. A number of cases have led to serious adverse reactions including fatalities.

WHO wishes to make the Rapid Alert Form available in more languages and to engage more Member States in use of the system. Closer links with pharmacovigilance reporting will be developed. Further collaboration with WHO prequalified laboratories will be encouraged. Extending the Rapid Alert Form to other stakeholders including procurement organizations, nongovernment organizations and other relevant stakeholders is under consideration in an effort to achieve a more complete assessment of the situation.

Conclusion

Once sufficient reports are received within the database, WHO will be in a position to report validated findings on a geographic or thematic basis. Reporting should begin to identify supply chain vulnerabilities and the finished medical products and active pharmaceutical ingredients most at risk of falsification and misrepresentation. This reporting will influence recommendations for market surveillance, increased vigilance and the development of sound strategies to minimize the risk from SSFFC products.
Safety and Efficacy Issues

Azithromycin: potential risk of QT prolongation

Singapore — Two recent research studies have strengthened the evidence regarding the potential risk of QT prolongation associated with the use of azithromycin. In the light of this latest data, healthcare professionals are advised to be aware of the risk of torsades de pointes and fatal arrhythmia when considering azithromycin as a treatment option for patients who are at risk for cardiovascular events. These patient groups include (1):

- Patients with known prolongation of the QT interval, a history of torsades de pointes and fatal arrhythmia, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure.
- Patients on drugs known to prolong the QT interval.
- Patients with ongoing pro-arrhythmic conditions such as uncorrected hypokalaemia or hypomagnesaemia, clinically significant bradycardia, and patients receiving Class IA (quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmic agents.
- Elderly patients and patients with cardiac disease who may be more susceptible to the effects of arrhythmogenic drugs on the QT interval.

Azithromycin is an azalide, a subclass of macrolide antibiotics derived from erythromycin that is widely used both orally and intravenously for the treatment of upper and lower respiratory tract infections and other infections involving susceptible organisms. There are currently 17 registered azithromycin-containing products in Singapore, including the Zithromax® range of products, Zmax® and 11 other generic products.

Although closely related, macrolide drugs such as erythromycin and clarithromycin are known to increase the risk of serious ventricular arrhythmias and are associated with an increased risk of sudden cardiac death. Azithromycin has previously been reported to be better tolerated than other macrolides, and has minimal side effects (2). However, within the last year, two research studies have provided evidence on the risk of QT prolongation associated with azithromycin.

One of the studies published in the New England Journal of Medicine (3) in May 2012 suggested a higher risk of cardiovascular deaths and deaths from any cause in persons treated with a five-day course of azithromycin compared to persons treated with amoxicillin, ciprofloxacin, or no drug. There were some limitations to this study, such as potential bias due to lack of randomization to the antibacterial drugs, outpatient setting investigation where it is likely that few patients were treated for severe or life-threatening infections, and the method of determination of cardiovascular deaths through death certificates instead of full medical records. Despite these, the study was noted to be methodologically sound and supportive of the validity of the overall findings.

The estimated excess risk of cardiovascular death compared with amoxicillin varied considerably with patient baseline cardiovascular risk, from roughly one in...
111,000 among healthier patients to one in 4100 among high-risk patients. The duration of the elevated risk of all-cause mortality and of cardiovascular death corresponded to the duration of azithromycin therapy. The increase in total deaths was determined to be attributed to cardiovascular deaths and not from other causes. The excess risk of cardiovascular death, especially of sudden death, was consistent with arrhythmias from drug-related QT prolongation.

The manufacturer of azithromycin also conducted a randomized, placebo-controlled parallel trial to assess the effects of azithromycin on the QT interval in 116 healthy adults (1). These subjects received either chloroquine (1000 mg) alone or in combination with azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-administration of azithromycin increased the QTc* interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF** were 5ms (10), 7ms (12) and 9ms (14) with the co-administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.

The US FDA has updated the azithromycin package inserts to strengthen the warnings and precautions section with information related to the risk of QT interval prolongation and Torsades de Pointes (4) Information regarding the results of the clinical QT study which showed that azithromycin can prolong the QTc interval has also been added.

References
4. FDA Drug Safety Communication, Azithromycin (Zithromax® or Zmax®) and the risk of potentially fatal heart rhythms at http://www.fda.gov/drugs/drugsafety/ucm341822.htm

Osteoporosis treatments: atypical femur fracture

New Zealand — In November 2009, Medsafe highlighted an association between alendronate and low-energy femoral shaft fracture (1).

Since then, similar cases have been published involving other bisphosphonates as well as denosumab (Prolia®).
Denosumab is a new treatment for osteoporosis that is approved but not currently available in New Zealand. Information on this risk is included in the data sheets for alendronate (Fosamax®), zolendronate (Zometa®) and pamidronate (Pamisol®).

To date there has been no confirmed association between strontium, teriparatide, raloxifene or hormone replacement therapy and atypical fractures of the femur.

Features associated with subtrochanteric and diaphyseal fractures include (2):

- Minimal to no trauma.
- Transverse fracture line on radiography.
- Prodromal pain.
- Unilateral cortical beaking and bilateral thickened diaphyseal cortices on radiography.
- Poor fracture healing.

The Centre for Adverse Reactions Monitoring (CARM) has received two reports of fractures describing some of the features outlined above. In both cases, the patient was taking alendronate.

Atypical subtrochanteric fractures are rare, less than 0.1% of total fractures in a New Zealand study (3). For a population of 10,000 patients at high risk of fracture, bisphosphonate treatment might be expected to prevent 108 hip fractures (and around 750 other fractures) per year and result in three subtrochanteric fractures (2). Therefore, the benefit risk ratio for bisphosphonate treatment remains favourable.

In patients with atypical femoral fractures, bisphosphonate treatment should be considered as a possible cause. Interruption of bisphosphonate therapy may be necessary for fracture healing. Re-treatment should be considered if bone density again begins to fall and after a discussion of the benefits and risks with the patient.

References

Ezogabine: retinal abnormalities and blue skin discoloration

United States of America — The Food and Drug Administration (FDA) has reported that ezogabine (Potiga®) can cause blue skin discoloration and eye abnormalities characterized by pigment changes in the retina. The FDA does not currently know if these changes are reversible. All patients taking ezogabine should have a baseline eye exam, followed by periodic eye exams.

Pigment changes in the retina have the potential to cause serious eye disease with loss of vision. It is not yet known whether the retinal pigment changes caused by ezogabine lead to visual impairment, although several patients have been reported to have impaired visual acuity.

The skin discoloration in the reported cases appeared as blue pigmentation, predominantly on or around the lips or in the nail beds of the fingers or toes, but more widespread involvement of the face and legs has also been reported. Scleral and conjunctival discoloration,
on the white of the eye and inside eyelids, has been observed as well. Skin discoloration generally occurred after four years of treatment with ezogabine, but has appeared sooner in some patients. Retinal abnormalities have also been observed in the absence of skin discoloration.

In light of this new safety information, all patients taking ezogabine or about to start, should have an eye exam followed by periodic eye exams thereafter. Ezogabine should be discontinued if ophthalmic changes are observed unless no other treatment options are available. If a patient develops skin discoloration, serious consideration should be given to changing to an alternate medication.


Incretin mimetics: risk of pancreatitis and pancreatic duct metaplasia

United States of America — The Food and Drug Administration (FDA) is evaluating unpublished new findings that suggest an increased risk of pancreatitis and pancreatic duct metaplasia in patients with type 2 diabetes treated with incretin mimetics. These findings were based on examination of a small number of pancreatic tissue specimens taken from patients after they died from unspecified causes.

Drugs in the incretin mimetic class include exenatide (Byetta®, Bydureon®), liraglutide (Victoza®), sitagliptin (Januvia®, Janumet®, Janumet XR®, Juvisync®), saxagliptin (Onglyza®, Kombiglyze XR®), alogliptin (Nesina®, Kazano®, Oseni®), and linagliptin (Tradjenta®, Jentadueto®). These drugs work by mimicking the incretin hormones that the body usually produces naturally to stimulate the release of insulin in response to a meal. They are used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.

The FDA has not reached any new conclusions about safety risks with incretin mimetic drugs but intends to obtain and evaluate this new information following participation in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Cancer Institute’s (NCI) Workshop on Pancreatitis-Diabetes-Pancreatic Cancer held in June 2013 to gather and share additional information.


Incretin mimetics and GLP-1-based therapies: pancreatic risks

European Union — The European Medicines Agency (EMA) is investigating findings by a group of independent academic researchers that suggest an increased risk of pancreatitis and pancreatic duct metaplasia in patients with type 2 diabetes treated with glucagon-like peptide 1 (GLP-1) based therapies (GLP–1 agonists and dipeptidylpeptidase-4 (DPP–4) inhibitors).

The findings are based on examination of a small number of pancreatic tissue samples obtained from organ donors with and without diabetes mellitus, who died due to causes other than diabetes. The Agency’s Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC) are currently investigating the information provided by the researchers to determine the need for possible further regulatory action.

The Agency has not reached any conclusions on this investigation. There is currently no change to the recommendations on the use of these medicines and no need for patients to stop taking their medicines.
Corticosteroid tapering should be implemented cautiously, particularly in patients with 4–6 human leukocyte antigen (HLA) mismatches. The product information will be updated to include a warning on rapid tapering of corticosteroids in patients with high immunologic risk and provide information on the corticosteroid doses used and the populations included in the clinical studies supporting the approval of Nulojix®.

Nulojix® in conjunction with basiliximab induction, mycophenolate mofetil and corticosteroid taper to 5 mg/day by week 6 post-transplant, has been associated with an increased rate of acute rejection, particularly Grade III rejection in the postmarketing setting. These Grade III rejections occurred in patients with 4 to 6 HLA mismatches. This corticosteroid taper was more rapid than that used in the clinical studies supporting the approval of Nulojix®.


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**Cinacalcet: fatal paediatric hypocalcaemia**

**United Kingdom** — A fatal case with severe hypocalcaemia has occurred in a paediatric investigational study of cinacalcet (Mimpara®). The manufacturer has suspended dosing, screening and enrolment in all paediatric cinacalcet investigational studies and is investigating this case to determine if any additional action is necessary.

Cinacalcet is approved only in adults. The product information warns of the risk of hypocalcaemia associated with cinacalcet. Therefore, patients should be carefully monitored for the occurrence of hypocalcaemia.

Cinacalcet is indicated for the treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease.
Cinacalcet may be used as part of a therapeutic regimen including phosphate binders and/or vitamin D sterols, as appropriate.

Cinacalcet is also indicated for the reduction of hypercalcaemia in patients with parathyroid carcinoma, or primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines) but in whom parathyroidectomy is not clinically appropriate or is contraindicated.


### Cilostazol-containing medicines: restricted use

**European Union** — The Committee on Medicinal Products for Human Use (CHMP) has recommended that the use of cilostazol-containing medicines in the treatment of intermittent claudication should be restricted. Cilostazol-containing medicines are available in the EU under the names Pletal® and Ekistol®.

The recommendations follow a review of current evidence which indicates that the modest benefits of these medicines are only greater than their risks in a limited subgroup of patients.

The Committee recommended that cilostazol should only be used in patients whose symptoms have not improved despite prior lifestyle changes. In addition, cilostazol-containing medicines should not be used in patients who have suffered severe tachyarrhythmia or recent unstable angina, heart attack or bypass surgery, or who take two or more antiplatelet or anticoagulant medicines such as aspirin and clopidogrel.

The Spanish Agency for Medicines and Health Products (AEMPS) asked the CHMP to carry out a review of these medicines following a number of reports of serious suspected side effects, in particular affecting the heart, as well as cases of serious bleeding.

**References**


### Aqueous cream: skin irritation

**United Kingdom** — Aqueous cream is a widely used product topically applied as an emollient for the symptomatic relief of dry skin conditions such as atopic eczema, and as a soap-substitute for skin washing.

Although aqueous cream is useful as a leave-on emollient in a substantial proportion of patients with eczema, it is known that in some patients, especially in children, it can cause skin reactions, such as stinging, burning, itching and redness.

In light of new information from the published literature all data on the benefits and risks of aqueous cream, particularly when used in children with eczema, have been recently reviewed in the UK (1). An audit of 100 children attending a paediatric dermatology clinic reported that aqueous cream emollient was associated with an immediate skin reaction (stinging, burning, itching, and redness) within 20 minutes in 56% of exposures, compared with 18% with other emollients used (2). Furthermore, several studies reported alterations in skin physiology (thinning of the outermost layer of the skin and increased skin water loss) following application of aqueous cream as an emollient in adults, both with
and without eczema (3, 4). A summary of all the evidence reviewed is available in the public assessment report (5).

The causative agent may be sodium lauryl sulfate (SLS), contained in emulsifying wax which is one of the ingredients of aqueous cream. SLS functions as a stabilizer and cleansing agent and is a known skin irritant. However, aqueous cream products often contain other ingredients such as chlorocrescol, cetostearyl alcohol and parabens, which may also cause or contribute to adverse skin reactions.

Despite the potential irritant effects reported in the literature, in clinical practice aqueous cream used both as an emollient and a wash-off soap substitute has been useful in a substantial proportion of patients with atopic eczema.

On the basis of the review, aqueous cream labelling and the information leaflet will be updated with a warning on the potential of local skin reactions, and SLS will be listed as an ingredient (6–7).

References


Zolpidem products: lower doses recommended

United States of America — The Food and Drug Administration (FDA) has approved label changes specifying new dosing recommendations for zolpidem products (Ambien®, Ambien CR®, and Edluar®) because of the known risk of next-morning impairment.

FDA has also warned that patients who take the sleep medication zolpidem extended-release (Ambien CR®) — either 6.25 mg or 12.5 mg — should not drive or engage in other activities that require mental alertness the day after taking the drug because zolpidem levels can remain high the next day.

Also included in the updated label are the dosing recommendations previously published on 10 January 2013 in FDA Drug Safety Communication. The recommended initial dose of certain immediate-release zolpidem products (Ambien and Edluar®) is 5 mg for women and either 5 mg or 10 mg for men. The recommended initial dose of zolpidem extended-release (Ambien CR®) is 6.25 mg for women and either 6.25 or 12.5 mg for men. If the lower doses (5 mg for immediate-release, 6.25 mg for extended-release) are not effective, the dose can be increased to 10 mg for immediate-release products and 12.5 mg for zolpidem extended-release. However, use of the higher dose can increase the risk of next-day impairment of driving and other activities that require full alertness.

Valproate-related products: risks during pregnancy

United States of America — The Food and Drug Administration (FDA) has alerted healthcare providers and patients that medications including and related to valproate sodium can cause decreased IQ scores in children whose mothers took the medication during pregnancy. Therefore, these drugs are being contraindicated for migraine headaches. Valproate products include valproate sodium (Depacon®), divalproex sodium (Depakote®, Depakote CP®, and Depakote ER®), valproic acid (Depakene® and Stavzor®), and their generics.

Valproate products have several FDA-approved uses including: prevention of migraine, treatment of epilepsy and treatment of manic episodes associated with bipolar disorder. Women who can become pregnant should not use valproate unless it is essential to managing their medical condition.

Medicines that contain valproate already have a boxed warning for foetal risk, including birth defects. The recently published Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study found further evidence of the IQ risk.


Thalidomide: risk of second primary malignancies

Canada — Health Canada has informed healthcare professionals of important new safety information which has been added to the Product Monograph for thalidomide capsules (Thalomid®).

Thalidomide is an immunomodulatory agent indicated for the treatment of patients who are 65 years of age or older with previously untreated multiple myeloma, in combination with melphalan and prednisone.

Second primary malignancies, in particular, acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), have been observed in an ongoing clinical trial in patients with previously untreated multiple myeloma receiving the combination melphalan, prednisone and Thalomid® (MPT). AML and MDS have been rarely reported in the post-market setting.

Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies.


Botulinum toxin type B: serious risks

United Kingdom — Botulinum toxin type B (Neurobloc®) is indicated only for the treatment of cervical dystonia in adults. The Medicines and Healthcare Products Regulatory Agency (MHRA) recommends that prescribers adhere to the licensed indication as its safety outside these circumstances has not been established. Cases of the known rare risk of toxin spread have been reported with all botulinum toxin products. Importantly, the cases with botulinum toxin type B were mostly reported with its off-label use.

All patients receiving any product containing botulinum toxin should be warned of the signs and symptoms of toxin spread, such as muscle weakness and breathing difficulties, and be advised to seek medical attention immediately if they experience breathing difficulties, choking, or any new or worsening swallowing difficulties, as such side effects may be life-threatening.
Magnesium sulphate during pregnancy: teratogenic effects

United States of America — The Food and Drug Administration (FDA) has advised healthcare professionals against using magnesium sulfate injection for more than 5–7 days to stop pre-term labor in pregnant women. This use of the drug is off-label. Administration of magnesium sulfate injection to pregnant women longer than 5–7 days may lead to low calcium levels and bone problems in the foetus, including osteopenia and fractures.

Magnesium sulfate is approved to prevent seizures in pre-eclampsia and for control of seizures in eclampsia.


Varenicline and buproprion: revision to consumer information

Canada — Health Canada has informed healthcare professionals that new information for varenicline tartrate (Champix®) and buproprion hydrochloride (Zyban®) has been added to the product information to indicate that nicotine replacement therapy (patches, gum, lozenges, etc.) should be considered before taking non-nicotine medicines.

This revision was based on available information about the treatments used to help people stop smoking. Nicotine replacement therapy should be considered before non-nicotine replacement.


Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious or unexpected adverse drug reactions. A signal is defined as “reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information”. All signals must be validated before any regulatory decision can be made.
Regulatory Action and News

Recommended influenza virus vaccine composition: 2013–2014 Northern hemisphere season

**Wold Health Organization** — It is recommended that vaccines for use in the 2013–2014 influenza season (Northern hemisphere Winter) contain the following:

- An A/California/7/2009 (H1N1)pdm09-like virus (A/Christchurch/16/2010 is an A/California/7/2009-like virus).

- An A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011 (A/Texas/50/2012 is an A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011). It is recommended that A/Texas/50/2012 is used as the A(H3N2) vaccine component because of antigenic changes in earlier A/Victoria/361/2011-like vaccine viruses (such as IVR-165) resulting from adaptation to propagation in eggs.

- A B/Massachusetts/2/2012-like virus.

- It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Brisbane/60/2008-like virus (B/Brisbane/33/2008 is a B/Brisbane/60/2008-like virus).

As in previous years, national or regional authorities approve the composition and formulation of vaccines used in each country. National public health authorities are responsible for making recommendations regarding use of the vaccine.

**Reference:** *Weekly Epidemiological Record*, 8 March 2013, vol. 88, 10 (pp. 101–116) at http://www.who.int/wer

Counterfeit antimalarial medicines: detection tool

**United States of America** — The Food and Drug Administration (FDA) has announced a public-private partnership to identify counterfeit or substandard antimalarial medicines, including falsified products, with the deployment of the FDA-developed Counterfeit Detection Device, called CD-3.

Globally, malaria kills more than 660,000 people annually, mostly children. The threat of drug resistance, limited availability of medication and increased presence of counterfeit or substandard antimalarial medicines pose significant challenges to treating this disease. Compromised antimalarials often have too little or no active ingredients, preventing adequate and timely treatment. Antimalarial medicines made with reduced dosages of active ingredients will not cure patients, and they can lead to resistant strains of the parasite, making it tougher to treat, even with authentic medicines.

The FDA has established a partnership with the Skoll Global Threats Fund, the U.S. Pharmacopeia (USP), the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the multi-agency President’s Malaria Initiative (PMI), led by the U.S. Agency for International Development (USAID).

The partnership will focus on testing and optimizing the use of the handheld CD-3 to identify counterfeit or substandard antimalarial medicines, including falsified products, in Africa and parts of Southeast Asia where the rates of malaria infection are high and where counterfeit antimalarial medicines are prevalent.
The effectiveness of the tool in detecting counterfeit or substandard versions of two common antimalarial therapies will be tested in Ghana in 2013 and 2014. Making detection technology more accessible to low and middle income countries would be invaluable in controlling the trade in counterfeit, falsified, or substandard medicines.


Black triangle for medicines subject to additional monitoring

European Union — The European Medicines Agency (EMA) has published an initial list of medicines that are subject to additional monitoring. This represents a deliverable of the new European pharmacovigilance legislation. These medicines will have to display an inverted back triangle in their package leaflet and in the summary of product characteristics (SmPC), together with a short sentence explaining what the triangle means.

All medicines on the European Union market are carefully monitored. If a medicine is labelled with the inverted black triangle, it does not mean that it is unsafe; the purpose of the symbol is to actively encourage healthcare professionals and patients to report any suspected adverse reactions observed with the medicine, either because the medicine is new to the market or because there is a limitation to the data available on its safety. Medicines subject to additional monitoring are:

- Medicines authorized after 1 January 2011 that contain a new active substance.
- Biological medicines for which there is limited post-marketing experience.
- Medicines with a conditional approval or approved under exceptional circumstances.
- Medicines for which the marketing-authorization holder is required to carry out a post-authorization safety study (PASS).

Other medicines can also be placed under additional monitoring, based on a recommendation from the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC). A medicine can be included on this list when it is approved for the first time or at any time during its lifecycle. It remains under additional monitoring for five years or until the PRAC decides to remove it from the list usually because studies have further established the safety profile of the product concerned. The complete additional-monitoring list will be reviewed every month by the PRAC and published on the EMA web site, where additional information on monitoring can also be found in all EU languages.

The inverted black triangle will start appearing in the package leaflet and SmPC of the medicines concerned from the autumn of 2013.


Levothyroxine: licence suspension

United Kingdom — The Medicines and Healthcare Products Regulatory Agency (MHRA) has suspended the licence for levothyroxine 100 microgram tablets for patients with hypothyroidism. This follows manufacturing difficulties and concerns that the product might not be interchangeable with other available levothyroxine 100 mcg tablets.

The decision to suspend follows a review by the Commission on Human Medicines (CHM), the MHRA’s independent advisory body, of manufacturing issues and sporadic reports of loss of control of hypothyroidism when switching between products.
Pregnant women, those with heart disease and those under treatment with levothyroxine following treatment for thyroid cancer may be particularly susceptible to changes in thyroid stimulating hormone and may require close monitoring by their doctor.


Strontium ranelate: restricted use

European Union — The Committee for Medicinal Products for Human Use (CHMP) has recommended a restriction in the use of the osteoporosis medicine strontium ranelate (Protelos/Osseor®), following an assessment of data showing an increased risk of serious heart problems. The CHMP recommended that Protelos/Osseor® should only be used to treat severe osteoporosis in postmenopausal women at high risk of fracture and severe osteoporosis in men at increased risk of fracture. Additional measures, including restrictions in patients with heart or circulatory problems, were also recommended to minimize the heart risks of these medicines. Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease or cerebrovascular disease or if hypertension becomes uncontrolled.

The CHMP recommendation is based on the advice of the Pharmacovigilance Risk Assessment Committee (PRAC).


Tetrazepam-containing medicines: suspension

European Union — The Coordination Group for Mutual Recognition and Decentralized Procedures: Human (CMDh) has endorsed the Pharmacovigilance Risk Assessment Committee (PRAC) recommendation to suspend the marketing authorizations of tetrazepam-containing medicines across the European Union (EU). The CMDh, a body representing Member States, is responsible for ensuring harmonized safety standards for medicines authorized via national marketing authorization procedures.

Tetrazepam, a medicine of the benzodiazepine class, is used in several Member States to treat painful contractures and spasticity. The review of tetrazepam was triggered by the French National Agency for the Safety of Medicine and Health Products (ANSM), following reports of serious skin reactions with this medicine in France.

Having assessed all available data on the risk of skin reactions, the PRAC concluded that tetrazepam is associated with a low but increased risk of serious skin reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis and DRESS syndrome) compared with other benzodiazepines. The Committee also noted that the available data on the effectiveness of tetrazepam were not sufficiently robust to support its use for the authorized indications.


Dabigatran etexilate: updated contraindications

European Union — On 25 April 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the contraindication for dabigatran etexilate (Pradaxa®).
Contraindications for Pradaxa® are now:

- Hypersensitivity to the active substance or to any of the excipients.
- Severe renal impairment (CrCl < 30 mL/min).
- Active clinically-significant bleeding.
- Lesion or condition, if considered a significant risk factor for major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under the circumstances of switching therapy to or from Pradaxa® (or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.
- Hepatic impairment or liver disease expected to have any impact on survival.
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, tacrolimus and dronedarone.
- Prosthetic heart valves requiring anticoagulant treatment.


Idebenone: voluntary withdrawal

Canada — Health Canada has informed healthcare professionals of the manufacturer’s decision to voluntarily withdraw idebenone (Catena®) from the Canadian market, as of 30 April 2013.

The withdrawal is based on the negative outcome of additional confirmatory efficacy studies required by Health Canada and is not the result of a specific safety concern. Prescribers are advised to discuss alternative treatment options with their patients.

Idebenone was authorized with conditions in Canada in July 2008 on the basis of promising evidence of clinical safety and efficacy in the symptomatic management of patients with Friedreich Ataxia. One of the conditions of authorization was to provide confirmatory evidence of efficacy in further clinical studies. However, the additional studies completed to date failed to meet their primary efficacy endpoint. The manufacturer will not recall Catena® currently prescribed.


Autologous chondrocyte implantation approved for cartilage defects

European Union — The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended marketing authorization for Maci® (matrix-induced autologous chondrocyte implantation), an advanced-therapy medicinal product (ATMP), for the repair of symptomatic, full-thickness cartilage defects of the knee in skeletally mature adult patients.

Cartilage has a poor ability to repair itself when injured. Injuries to the smooth cartilage surface of the knee joint increase rubbing and friction in the knee and predispose the knee to
A number of surgical procedures aiming to repair cartilage have been developed to treat patients with articular cartilage defect of the knee. One of them is autologous chondrocyte implantation (ACI), a therapy based on tissue engineering, which was first described in 1994. It uses chondrocytes, or cartilage cells, which are derived from the patient’s own cartilage, grown outside the patient’s body and then transplanted into the patient’s lesions after several weeks. The benefit of ACI over other restoration techniques is that larger lesions can be treated.

Maci® is a third-generation ACI product which uses a scaffold formed of porcine collagen on which autologous chondrocytes are seeded. At implantation, the scaffold is trimmed to the size and shape of the cartilage defect. The cells/collagen structure is held in place in the lesion with fibrin glue.


Vismodegib approved for basal cell carcinoma

European Union — The Committee for Medicinal Products for Human Use (CHMP) has recommended the granting of a conditional marketing authorization for vismodegib (Erivedge®) 150 mg, hard capsule, intended for the treatment of adult patients with symptomatic metastatic basal cell carcinoma (BCC) or locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy.

Vismodegib, an antineoplastic agent, is an orally available small-molecule which acts by blocking specific genes involved in proliferation, survival, and differentiation of cells. The benefits with Erivedge® are its ability to reduce lesion size or sum of the longest diameter of lesions more than 30% or to provide complete resolution of ulceration in all target lesions in 48% of the patients with locally advanced BCC and in 33% of the patients with metastatic BCC. The most common side effects are muscle spasms, alopecia, dysgeusia, weight decreased, fatigue and nausea. There is a high risk that vismodegib can cause embryo-foetal death or severe birth defects.


Lenalidomide: approved for myelodysplastic syndromes

European Union — The Committee for Medicinal Products for Human Use (CHMP) has recommended a variation to the terms of the marketing authorization for lenalidomide (Revlimid®).

The CHMP adopted a new indication for myelodysplastic syndromes. Revlimid® is now also indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.


Nimodipine oral solution approved for subarachnoid haemorrhage

United States of America — The Food and Drug Administration (FDA) has approved Nymalize®, a new nimodipine oral solution to treat patients with
symptoms resulting from subarachnoid haemorrhage. Nimodipine was previously available only as a liquid-filled gel capsule.

The FDA has received reports of serious and sometimes fatal consequences from intravenous (IV) injection of the liquid contents of oral nimodipine capsules. IV administration of nimodipine meant for oral use can result in death, cardiac arrest, severe decreases in blood pressure and other heart-related complications.

The approval of Nymalize® is based on clinical studies evaluating the use of nimodipine oral capsules in patients with subarachnoid haemorrhage. The most common adverse event observed in the studies was decreased blood pressure.


Golimumab approved for ulcerative colitis

United States of America — The Food and Drug Administration (FDA) has approved a new use for golimumab (Simponi®) injection to treat adults with moderate to severe ulcerative colitis.

Golimumab works by blocking tumour necrosis factor (TNF). Previously approved to treat rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, Simponi® is now approved to treat adults with moderate to severe ulcerative colitis that is refractory to prior treatment or requires continuous corticosteroid therapy.

The most common side effects in patients treated with Simponi® are upper respiratory infection and redness at the site of injection. Patients treated with Simponi® are at increased risk of developing serious infections, invasive fungal infections, reactivation of Hepatitis B infection, lymphoma, heart failure, nervous system disorders and allergic reactions.


Radium dichloride approved for advanced prostate cancer

United States of America — The Food and Drug Administration (FDA) has approved radium $^{223}$Ra dichloride (Xofigo®) to treat men with symptomatic metastatic castration-resistant prostate cancer that has spread to bones but not to other organs. It is intended for men whose cancer has spread after receiving medical or surgical therapy to lower testosterone.

The most common side effects reported during clinical trials in men receiving Xofigo® were nausea, diarrhoea, vomiting and swelling of the leg, ankle or foot. The most common abnormalities detected during blood testing included anemia, lymphocytopenia, leukopenia, thrombocytopenia, neutropenia.


Erlotinib and diagnostic test approved for non-small cell lung cancer

United States of America — The Food and Drug Administration (FDA) has approved the cobas EGFR Mutation Test, a companion diagnostic for the cancer drug erlotinib (Tarceva®). This is the first FDA-approved companion diagnostic that detects epidermal growth factor receptor (EGFR) gene mutations, which are present in approximately 10 percent of non-small cell lung cancers (NSCLC).

The test is being approved with an expanded use for erlotinib as a first-line treatment for patients with NSCLC that
has metastasized and who have certain mutations in the EGFR gene.

The FDA approved Tarceva® on 16 April 2010 for maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.


Dabrafenib, trametinib and companion diagnostic test for advanced skin cancer

United States of America — The Food and Drug Administration (FDA) has approved two drugs, dabrafenib (Tafinlar®) and trametinib (Mekinist®), for patients with metastatic or unresectable melanoma.

Tafinlar®, a BRAF inhibitor, is approved to treat patients with melanoma whose tumours express the BRAF V600E gene mutation. Mekinist®, a MEK inhibitor, is approved to treat patients whose tumors express the BRAF V600E or V600K gene mutations. Approximately half of melanomas arising in the skin have a BRAF gene mutation. They are being approved as single agents, not as a combination treatment.

The FDA has approved Tafinlar® and Mekinist® with a genetic test called the THxID BRAF test®, a companion diagnostic that will help determine if a patient’s melanoma cells have the V600E or V600K mutation in the BRAF gene.

Dabrafenib includes hyperkeratosis, headache, fever, joint pain, non-cancerous skin tumors, hair loss and hand-foot syndrome.

The most serious side effects reported in patients receiving Mekinist® included heart failure, lung inflammation, skin infections and loss of vision. Common side effects included rash, diarrhea, peripheral edema and skin breakouts that resemble acne.

Women of child bearing years should be advised that Tafinlar® and Mekinist® carry the potential to cause foetal harm. Men and women should also be advised that these products carry the potential to cause infertility.


Cysteamine bitartrate approved for rare genetic condition

United States of America — The Food and Drug Administration (FDA) has approved cysteamine bitartrate (Procysbi®) for the management of nephropathic cystinosis in children and adults.

Cystinosis is a rare genetic condition that affects an estimated 500 patients in the United States and about 3000 patients worldwide. Cystinosis may lead to slow body growth and small stature, weak bones and developing and worsening kidney failure.

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Regulatory Action and News


**Fluticasone furoate and vilanterol approved for chronic obstructive pulmonary disease**

**United States of America** — The Food and Drug Administration (FDA) has approved fluticasone furoate and vilanterol inhalation powder (Breo Ellipta®) for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It is also approved to reduce exacerbations of COPD in patients with a history of exacerbations.

The drug carries a boxed warning that long-acting beta2-adrenergic agonists (LABAs) increase the risk of asthma-related death. The safety and efficacy of Breo Ellipta® in patients with asthma have not been established, and it is not approved for the treatment of asthma.

Breo Ellipta® may cause serious side effects, including increased risks of pneumonia and bone fractures. The most common side effects reported included nasopharyngitis, upper respiratory tract infection, headache, and oral candidiasis.


**Oxycodone with abuse-deterrent properties approved**

**United States of America** — The Food and Drug Administration (FDA) has approved updated labelling for reformulated oxycodone hydrochloride controlled-release tablets (OxyContin®). The new labelling indicates that the product has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route.

Additionally, because original OxyContin® provides the same therapeutic benefits as reformulated OxyContin®, but poses an increased potential for certain types of abuse, the FDA has determined that the benefits of original OxyContin® no longer outweigh its risks and has been withdrawn from sale. Accordingly, the agency will not accept or approve any abbreviated new drug applications (generics) that rely upon the approval of original OxyContin®.

The reformulated tablet is more difficult to crush, break, or dissolve. It also forms a viscous hydrogel and cannot be easily prepared for injection.


**Imatinib approved for leukaemia**

**European Union** — The Committee for Medicinal Products for Human Use (CHMP) has recommended granting of a marketing authorization for imatinib (Imatinib Accord®), film-coated tablet 100 mg and 400 mg intended for the treatment of leukaemia.

Imatinib is a small molecule protein-tyrosine kinase inhibitor that potently inhibits the activity of the Bcr-Abl tyrosine kinase (TK), as well as several receptor TKs. Imatinib Accord® is indicated for the treatment of:

- Paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment.
- Paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
- Adult patients with Ph+ CML in blast crisis.
First A1c test labelled for diagnosing diabetes

United States of America — The Food and Drug Administration (FDA) has announced that it is allowing marketing of the Tina-quant HbA1cDx assay (Cobas Integra 800 Tina-quant HbA1cDx assay®) for the diagnosis of diabetes by healthcare professionals.

The HbA1c tests, or A1c tests, currently on the market are FDA-cleared for monitoring a patient’s blood glucose control, but not for diagnosing diabetes. A1c tests measure the percentage of hemoglobin A1c that is bound to glucose, giving a patient’s average glucose level over a three-month period.

The diagnostic criteria for diabetes have changed over time. Based on the research and recommendations of international diabetes experts, many health care providers have already been using some A1c tests to diagnose diabetes, in addition to the established diagnostic procedures of a fasting blood glucose test and an oral glucose tolerance test to diagnose diabetes.

However, before now, A1c tests were not specifically designed or granted permission by FDA to be marketed for diabetes diagnosis, making it difficult to know which A1c tests were accurate enough for this purpose. The Tina-quant HbA1cDx assay, a laboratory-based test, can be used to both accurately diagnose diabetes and monitor blood glucose control.

Over-the-counter HbA1c tests should not be used by patients to diagnose diabetes, and only a qualified health care professional should make a diagnosis of diabetes. Individuals who receive a diabetes diagnosis should discuss with their physician what they need to do to manage their diabetes.

Hemoglobin A1c tests, including the Tina-quant HbA1cDx assay, should not be used to diagnose diabetes during pregnancy and should not be used to monitor diabetes in patients with hemoglobinopathy, hereditary spherocytosis, malignancies, or severe chronic, hepatic and renal disease. This test should not be used to diagnose or monitor diabetes in patients with the hemoglobin variant hemoglobin F.

International Meeting of World Pharmacopoeias

A pharmacopoeia is a legally binding collection of standards and quality specifications for medicines used in a country or region. Within the pharmacopoeia, a quality specification is a set of appropriate tests that will confirm the identity and purity of the product, ascertain the strength (or amount) of the active substance and, when needed, the performance characteristics. Reference substances are used in testing to help ensure the quality, such as identity, strength and purity, of medicines.

A pharmacopoeia also covers pharmaceutical starting materials, excipients, intermediates and finished pharmaceutical products (FPPs). General requirements may also be given on important subjects related to medicines quality, such as analytical methods, microbiological purity, dissolution testing, or stability (1).

The role of a modern pharmacopoeia is to furnish quality specifications for active pharmaceutical ingredients (APIs), FPPs and general requirements. The existence of such specifications and requirements is necessary for the proper functioning or regulatory control of medicines production. Pharmacopoeial requirements form a basis for establishing quality requirements for individual pharmaceutical preparations.

According to the information available to the World Health Organization (WHO), 140 independent countries are at present employing thirty national as well as African, European and International Pharmacopoeias (2).

Compared to national and regional pharmacopoeias, The International Pharmacopoeia (Ph. Int.) is issued by WHO as a recommendation with the aim of providing international standards – including less technically demanding alternatives where needed – for adoption by Member States and to help achieve a potentially global uniformity of quality specifications for selected pharmaceutical products, excipients and dosage forms.

In response to a call for input, and as follow-up to discussions with representatives of world pharmacopoeias during the International Conference of Drug Regulatory Authorities in Hong Kong in 2002 and in Madrid in 2004, WHO organized the International Meeting of World Pharmacopoeias in early 2012. The aim was to discuss topics of common interest and address identified challenges.

In order to prepare for the meeting, WHO provided a set of preliminary questions on pharmacopoeias to meeting participants in an effort to inspire input to the agenda. The questions, presentations and final report are now available on a dedicated web site (3). This article is a summary of the report.

Pharmacopoeia: publication and frequency of updates

The pharmacopoeia, as a public tool, maintains quality of medicines by collecting the recommended procedures for analysis and specifications for the determination of pharmaceutical substances, excipients and dosage forms and, in most cases, consists of a general part (tests, methods and general requirements) and a specific part in the
Questions proposed to pharmacopoeias

1. Name of pharmacopoeia.
2. Is pharmacopoeia referred to in national/regional legislation – if yes, which?
3. Does national/regional legislation make reference to other national, regional, or international pharmacopoeias(s) – if yes, which?
4. When was publication of latest edition?
5. What is the update frequency – annually, biannually, other (please specify).
6. For which products does the pharmacopoeia provide specifications? APIs, dosage forms, herbal products, biologicals, traditional medicines, etc. (please specify)
7. What number of texts are included in the pharmacopoeia monographs for APIs, finished dosage forms, biologicals, and general monographs?
8. Is there collaboration with and/or being part of a (different) national/regional pharmacopoeia – if yes, which?
9. Is there publication of harmonized pharmacopoeial texts within the pharmacopoeia if yes, which pharmacopoeia, which type, how many?
10. Interaction with stakeholders, including regulators?
11. What is the strategy for the future?

Legal basis and references to other pharmacopoeias

Pharmacopoeias are referred to in legislation which confirms their legally binding status in the relevant country or region.

In Europe, a regional approach is used. the European Pharmacopoeia (Ph. Eur.) was created by eight Member States in 1964 and today consists of 36 Member States and the European Union (EU) which are signatories to the Convention on the Elaboration of a European Pharmacopoeia. Ph. Eur. members are: Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, (the former Yugoslav Republic of) Macedonia, Malta, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden,
Switzerland, Turkey, United Kingdom, and the EU. In addition, there are 24 observers, comprising 23 countries and WHO.

EU Directives stipulate that “the monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it. In respect of other substances, each Member State may require observance of its own national pharmacopoeia.” These directives are transposed into national legislation of EU Member States.

Some of the 36 Member States of the Ph. Eur. Convention have decided to discontinue their own national pharmacopoeia and use only the Ph. Eur. Examples are Sweden and Finland. Other Member States of the Ph. Eur. Convention have decided to continue their national pharmacopoeia for products of solely national interest. In Switzerland, for instance, the Pharmacopoea Helvetica (Ph. Helv.) exists alongside the Ph. Eur. and the two together form the legally binding pharmacopoeia. In France, the pharmacopoeia consists of the texts of the European Pharmacopoeia and of the French Pharmacopoeia, including the “overseas” pharmacopoeia. Other countries, such as the United Kingdom, have decided to fully integrate the texts of the Ph. Eur. into their national pharmacopoeia; hence the British Pharmacopoeia (BP) contains the texts of the Ph. Eur. in addition to the national texts of the BP.

National/regional legislation often includes reference to other pharmacopoeias in the event that their own pharmacopoeial texts are not available. Thus the EU pharmaceutical legislation and hence the legislation of all EU Member States includes references both at the national/regional and international levels. Historic and language ties also play a role. For example, the Portuguese pharmacopoeia is also accepted in legislation for Brazil and other countries where Portuguese is an official language.

WHO’s International Pharmacopoeia (Ph. Int.) is «ready for use» by Member States. The Ph. Int. is referred to in a number of national legislations due to its applicability.

**For which products does the pharmacopoeia provide specifications?**

A large number of products are usually covered, reflecting the diligence and commitment of pharmacopoeial authorities and their appointed experts to develop a comprehensive working tool with up-to-date scientific data. The complexity and diversity of most pharmacopoeias results from mutual integration and interdependence with monographs for various types of products such as active pharmaceutical ingredients (APIs), excipients, herbal products, biologicals (vaccines, blood products), radiopharmaceuticals, dosage forms and homeopathic preparations.

It may be noted that there is a majority of finished dosage forms, which generally can be defined as the form of active ingredient which is or is intended to be dispensed or administered to the patient and requires no further manufacturing or processing other than packaging and labelling. This is in parallel to the decreasing tendency of specific national monographs for APIs within some national pharmacopoeias due to replacement with monographs from regional or international pharmacopoeias.

As the pharmacopoeia itself has emerged from experience gained throughout the centuries, the roots of this valuable knowledge can still be seen in contemporary medicine as traditional medicine monographs, represented mainly in the pharmacopoeias of China, France (overseas), Japan and Ph. Eur.
Likewise, homeopathic approaches are represented in pharmacopoeias in Brazil, Germany and Mexico, for example.

The pharmacopoeias reviewed at the International Meeting of World Pharmacopoeias contain standards for chemical and biological drug substances, dosage forms, compounded preparations, excipients, medical devices and dietary supplements. During the current meeting some countries, such as Brazil, France, Germany, Mexico, Serbia and Switzerland, provided examples of incorporating a national formulary for hospital and/or community pharmacy preparations into their pharmacopoeias. In Portugal, there is a non-official national formulary which is published by the Portuguese Pharmacies Association. During the meeting, examples were given of types of monographs with less frequent occurrence than other types.

For example, monographs for blood products were presented by Argentina (12), Brazil (20) and India (21), while monographs for vaccines were presented by Argentina (21), India (57), Kazakhstan (15) and Ukraine (26). Homeopathic preparations described in monographs were presented mainly by France (320), Germany (120) and Mexico (558) and finally monographs for traditional medicine were given as an example by China (2165). A total of 92 herbal, traditional herbal and homeopathic monographs are present in the British Pharmacopoeia 2012. Supplementary information is included in some of the pharmacopoeias, for example general texts, reference tables, and texts on methods of analysis, reagents, materials/containers, sutures, and reference substances used in national monographs.

Collaboration among pharmacopoeias
Pharmacopoeial authorities collaborate at both regional and international levels for the sake of harmonization and exchange of experience. Active and passive forms of participation occur. Active participants, such as members of Ph. Eur., can contribute their share of pharmacopoeial development, while passive forms of participation may include observational missions to benefit from the experience of other countries in specific areas and gain access to the work on quality control of medicines and methods of analysis used.

Leading world pharmacopoeias promote constant progress within pharmacopoeial development, ”good pharmacopoeia practice” and recommendations of procedures for analysis intended to serve as source material for reference or adaptation by any of their Member States wishing to establish pharmaceutical requirements.

Ph. Int. provides an opportunity to comment on drafts by all world pharmacopoeias and offers participation in meetings, such as consultations and Expert Committees during the WHO consultation process. There are also WHO special projects covering quality assurance of medicines worldwide, such as collaboration with the African Pharmacopoeia, British Pharmacopoeia, Chinese Pharmacopoeia, Council of Europe/Ph. Eur. and the Pharmacopoeial Discussion Group (PDG).

Ph. Eur. covers all national pharmacopoeias of the signatory parties to the Convention, who are members of the Ph. Eur. with emphasis on complementarity, thereby reducing duplication of work. In some member countries of the Ph. Eur. national pharmacopoeias complement the Ph. Eur. for texts of interest to one Member State only. Some member countries also republish Ph. Eur. monographs in their national pharmacopoeias. Membership and observership enables States to participate in Ph. Eur. Commission sessions even if only Members are entitled to vote. Within these sessions, each Member State is represented by its national delegation consisting of not more
than three members. On all technical matters delegations cast a vote. The EU decides on behalf of EU Member States in all non-technical issues of the Ph. Eur. Each Member State and observer can also propose national experts for each group of experts or working party.

The European Medicines Agency (EMA) participates in the sessions of the Ph. Eur. Commission and working parties of interest. The European Directorate for the Quality of Medicines and HealthCare (EDQM) participates in relevant committees and working parties at the level of the EMA alongside national competent authorities. In addition, annual meetings are organized between EDQM and national pharmacopoeial authorities. Thirty-six Member States and the EU are signatories to the Convention on the Elaboration of a European Pharmacopoeia.

Observership to the Ph. Eur. allows for participation in the scientific work of the European Pharmacopoeia Commission. Observer examples are Belarus, Brazil, China, Russia, the United States of America, and WHO.

The Pharmacopoeial Discussion Group (PDG) consists of representatives of three pharmacopoeias: Ph. Eur., Japanese Pharmacopoeia (JP) and the United States Pharmacopoeal Convention (USP). Its main activities are retrospective harmonization of general chapters and excipient monographs. In addition, Ph. Eur. and USP are running a pilot project on prospective harmonization of active pharmaceutical ingredient monographs.

MERCOSUR, as an example of intensive collaboration at the regional level, and is formed by Argentina, Brazil, Paraguay and Uruguay. Texts and chapters are discussed for inclusion in the MERCOSUR Pharmacopoeia.

Some collaboration is historically and geographically related. Traditional collaboration of the Czech Republic with the Slovak Republic results from a common history. Agreements for collaboration have been signed between countries to increase the degree of compatibility, such as the USP with Mexico. Ukraine has also signed a collaborative agreement with USP, while intensely working with Kazakhstan. A memorandum of understanding has been signed by both the British Pharmacopoeia (BP) and Ph. Int. to use and incorporate developed monographs mutually.

Intensive collaboration with China’s pharmacopoeial authorities was described by representatives of the British and French Pharmacopoeias and USP during the meeting. France collaborates with Algeria, Morocco and Tunisia due to the fact that the French language is used in those pharmacopoeias. Brazil and Viet Nam are also named as collaborators with the French Pharmacopoeia. In information sent to WHO, Korean pharmacopoeial representatives mentioned bilateral memoranda of understanding with Ph. Eur. and USP.

**Publication of harmonized pharmacopoeial texts within the pharmacopoeia**

The PDG has defined harmonization of a pharmacopoeial monograph or general chapter as follows:

“...A pharmacopoeial general chapter or other pharmacopoeial document is harmonized when a pharmaceutical substance or product tested by the document’s harmonized procedure yields the same results and the same accept/reject decision is reached.” (4).

When using a fully harmonized pharmacopoeial monograph or general chapter, an analyst will perform the same procedures and reach the same accept/reject decisions irrespective of which PDG pharmacopoeia is referenced. This is called interchangeability and...
each pharmacopoeia identifies, in an appropriate manner, each fully harmonized monograph and general chapter.

The realization that it was important to have an independent evaluation of medicinal products before they are allowed on the market was reached at different times in different regions. In many cases action was driven by tragedies, such as that with sulfanilamide in the USA in 1937 and with thalidomide in the 1960s. Therefore, the urgent need to rationalize and harmonize regulation was impelled by concerns over rising costs of health care, escalation of the cost of research and development and the need to meet public expectations for a minimum delay in making safe and efficacious new treatments available to patients in need.

**Latin America**
Countries participating within MERCOSUR have included harmonized texts in their national pharmacopoeias after discussion. PDG texts are also considered during discussions of the Brazilian Pharmacopoeia Committee. Mexico does not have a formal process for the harmonization of information with other pharmacopoeias, but its drug monographs are consistent in their specifications with the BP, Ph. Eur. and USP in 60–100%.

Ph. Int. collaborates worldwide and has texts harmonized from various sources due to its rich collaboration. With the British Pharmacopoeia, this resulted in three texts adopted in 2010, with 19 in the pipeline. Also, through collaboration with PDG, 12 general methods were adopted in Ph. Int. in 2011 with more in the pipeline for methods of analysis and supplementary information.

**Interaction with stakeholders, including regulators**
There are many ways for national/regional pharmacopoeial authorities to interact and be influenced by stakeholders, particularly through public forums.

The most common interactions are at national level between national and regional regulatory authorities, quality control laboratories and different institutions related to quality assurance of medicines. Fusion of academic, clinical and industrial fields, such as universities and other academic bodies, hospital and community pharmacies organized in expert groups, and manufacturers worldwide through their organizations, represent a platform for comprehensive and progressive discussion.

To enable harmonization and a reliable
source of fluid information exchange at the global level, international organizations (UNAIDS, UNFPA, UNICEF, World Bank, WIPO, WTO, WCO), international professional and other associations, nongovernmental organizations (FIP, IFPMA, IGPA, MSF, WMA, WSMI), quality control laboratories (other than national/regional), United Nations-related organizations such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, and WHO programmes including International Nonproprietary Names, Prequalification of Medicines, Medicines Regulatory Support, Medicines Safety, Traditional Medicines, Quality, Safety and Standards and specific disease programmes, are all stakeholders in collaboration.

Specific harmonization issues are discussed within regional and inter-regional harmonization groups (ASEAN, GCC, ICH, PANDRH, SADC, etc.). To ensure discussion and pragmatic approaches, annual science and standard symposia are organized, as well as public forums, for an unbiased outside view on particular issues.

**Strategy for the future**

Strategies of the individual pharmacopoeias differ for geographical and economic reasons and depending on the level of integration to respective regional international systems. There was a commitment to establish comprehensive, updated editions with highly compatible standards at a national or regional level, as well as intentions to harmonize intensively with emphasis on increased quality assurance of medicines around the world.

**International**

Ph. Int. commits to fulfilling the mandate of WHO given by its Member States and responds to the needs of the latter. As an international body, it also responds to the needs of quality control laboratories for post-marketing surveillance and maintains the international applicability of Ph. Int. specifications. Keeping the costs of analysis in mind, especially in the case of developing countries, Ph. Int. provides standards for major public health needs.

**Regional**

Ph. Eur. supports innovation and flexibility without losing the aim of a pharmacopoeia to provide official, recognized and technically sound quality standards. It also remains at the forefront in the biofield and constantly increases pharmacopoeial harmonization through collaboration, i.e. as part of PDG, and maintains observers within other pharmacopoeial institutions worldwide. Ph. Eur. Member States Sweden and Finland continue to cooperate and be active in the elaboration of the Ph. Eur.

**National**

Croatia is currently preparing a publication of a new edition of the Croatian Pharmacopoeia.

The Czech Republic would like to complete a national formulary, mainly in the field of paediatrics through cooperation with the chamber of paediatricians. Assessment of stability in the pharmacopoeia formularies for small-scale products and products prepared in pharmacies have also been mentioned as a future plan by Czech representatives, as well as establishment of a new group of experts from hospital pharmacies and certified laboratories.

France presented its strategy for the future at both the national and European levels. Publication online will define new policy and reinforce the code of practice in line with the new French Public Health Law. France defines the work programme based on both interest of patients or professionals (paediatric, ophthalmic and homeopathic preparations) and conforms to regulation and national strategy (French overseas territories). As a key player within the Ph. Eur., France would like to contribute to specific topics such as biological products, cell
and tissue therapies, anti-allergenic products, antiseptic preparations, paediatric preparations, traditional herbal preparations and collaboration with P4 procedures.

In addition to its contribution to the Ph. Eur., Germany focuses on particular technical issues in terms of pharmaceutical analysis such as identification of materials by the evaluation of analytical fingerprinting, use of non-destructive spectroscopic methods, imaging techniques for the intact pharmaceutical preparations, trace analysis of impurities and simplified analytical identification tests for certified substances.

As a country collaborating closely with the Ph. Eur., Portugal is focusing on its future plan to update national texts and to tighten the links with Portuguese-speaking countries and stakeholders.

Serbia will prepare its national addition to Ph. Eur., update national “Magistral Formularies” and continue cooperation with the Ph. Eur.

Spain plans to follow the timetable for publication of the in-force Ph. Eur. successive editions (simultaneous translation), to work with internal Spanish groups that support work of the experts and specialists in European and international groups and continue its efforts to cooperate with the work of the Ph. Eur. and international groups.

Switzerland focuses on participation in the activities of the Ph. Eur. in the framework of the legally binding mandate of the Ph. Eur. Convention.

Introduction of quality standards of the Russian Federation Pharmacopoeia (SP RF) 12th edition (Vols 1–5) in the territory of the Russian Federation, development of new quality standards for medicinal products and review of the older ones, will help to upgrade the national regulatory system. Plans for the future also include harmonization of the SP RF monographs with the corresponding monographs of the leading world pharmacopoeias. This will be assisted by participation of the Federal State Budgetary Institution “Scientific Centre for Expert Evaluation of Medicinal Products” of the Ministry of Health of the Russian Federation in the work of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, work of the EDQM (as an observer) and work of the WHO Working Group on Good Pharmacopoeial Practices.

United Kingdom representatives presented priorities at the international level. Contributions and intensive collaboration within the Ph. Eur. were also described. National activities of the BP will focus on the Annual BP and BP (Vet) Publications, British Approved Names Supplements, increase in New Formulated Preparation Monographs (licensed and unlicensed), Supplementary Chapters for BP and BP (Vet), Red Tape Challenge, Stakeholder Cooperation (manufacturers, practitioners, pharmacies, etc.) and tailored publications.

Japan’s efforts toward internationalization of its pharmacopoeia are based on prompt publication and further improvement of the JP English edition and web site. Building up the framework for international information exchange among pharmacopoeias will also be intensified. For its next revision JP commits itself to follow-up of the revision of “General Rules for Preparations” in JP16: general quality tests for preparations would be newly set, containers and storage section revised, and a new framework for monographs of drugs created whose manufacturing processes are different, including impurities (including residual solvents), process-related substances, impurities in biotechnology products and tests for preparations.

China provided information to WHO stating that the country is committed to more cooperation with other world leading pharmacopoeias.
India, in terms of sharing of information among pharmacopoeias, would like to focus on resources, working in pockets where there is a need for sharing information and providing commitment to monitoring, harmonizing with leading pharmacopoeias. Provision of quality medicines will be improved through harmonized drug standards and monitoring the quality of medicines through an effective regulatory system.

Indonesia’s plans are to publish a new edition of the Indonesian Pharmacopoeia every five years, to publish the supplement annually for the existing pharmacopoeia and to publish the pharmacopoeia in an English version.

Korea has informed WHO that it aims to include in its pharmacopoeia all medicines which are relevant from the viewpoint of health care and medical treatment. It will revise it in a timely manner for more efficient application and will follow international harmonization. Transparency will be important in revision of the Korean Pharmacopoeia, and the document will be publicly available and include up-to-date analytical methods and preparation of reference standards.

**Eastern Europe**

A future strategy for Kazakhstan will include the introduction of the State Pharmacopoeia, further harmonization with Ph. Eur. and USP and development, edition and revision of its own monographs.

Ukraine would like to transform its status from observer at the Ph. Eur. Commission to membership, support leading pharmacopoeias and implement harmonized standards. It aims to facilitate the movement of high-quality medicines through developing pharmacopoeial educational programmes and expanding visiting scientist programmes.

**Latin America**

The priorities for Argentina’s Pharmacopoeial Commission are strengthening of regional harmonization through joint development of reference standards and harmonization of general methods and monographs in order to establish similar quality standards within the region.

Brazil commits to continuing its integration with the MERCOSUR Pharmacopoeia and aligning the Brazilian Pharmacopoeia with public health needs and public policy development.

Mexico wants to stay tuned to the needs of the health authority and users, to maintain its current pharmacopoeia, continue promoting the approach of users to participate in the development of monographs and establish closer communication with colleagues in other parts of the world.

**North America**

USP strategy focuses on creating monographs in ways that rely on both the traditional donor model as well as on research and development in its own laboratories. In support of the second approach, USP has created the Medicines Compendium (MC), a freely available, online-only compendium of public standards for medicines approved in any country. The MC monographs provide performance tests for critical quality attributes and acceptance criteria, a source-independent reference procedure and one or more acceptable procedures submitted by manufacturers.

The MC strives to make available reference materials for all possible impurities associated with a particular monograph, and to expand approaches to include USP-NF, where many monographs are missing and more need updating. USP is also strengthening its ability to develop impurity reference materials independently through synthetic capabilities.

In addition, USP is working on standards with allied activities in...
support of manufacturers, regulatory bodies and others. Examples include a “global comparator product”, as well as emphasis on biological medicines standards in support of new, biosimilar and interchangeable biological products.

USP is working on spectral imaging approaches that allow field approaches to assure identity. These latter efforts align with the more elaborate laboratory testing approaches in a pharmacopoeial monograph or a private specification.

**Conclusion**

Participants at the meeting agreed to focus in the future on acceleration of international harmonization between world pharmacopoeias, and also on the establishment of an international bank of harmonized texts for substances and finished dosage forms of the most common vital medicines. It was also agreed that there should be a build-up of frameworks for international information exchange among pharmacopoeias, an introduction of new techniques, including analytical fingerprinting, non-destructive spectroscopic methods and imaging. Lastly, support was reiterated for maintenance of the international applicability of Ph. Int. specifications.

Individual presentations, the full report and conclusions are to be found on the WHO web site (3).

**References**


Consortium to test kala-azar treatments in East Africa

The research and development project, AfriCoLeish, will run for three years and aims to test new treatments for kala-azar (visceral leishmaniasis, or VL) and co-infection of the disease with HIV in Ethiopia and Sudan.

The AfricoLeish project, Care Package for Treatment and Control of Visceral Leishmaniasis in East Africa, aims to develop and deliver a shorter combination treatment for kala-azar patients that is as safe and effective as the current WHO-recommended first-line treatment of sodium stibogluconate and paromomycin (SSG&PM). The project also aims to determine appropriate treatment strategies for kala-azar patients who are also HIV positive, in order to treat and prevent repetitive relapses that are common in co-infected patients.

Kala-azar is fatal if left untreated. An estimated 300,000 cases occur per year in 70 endemic countries. Estimates suggest there are 30,000 new cases per year in Africa, with numbers rising sharply during an epidemic. Existing monotherapies are toxic, costly, and difficult to administer, and the treatment duration is long, requiring extended hospital stays. Efficacious and cost-effective treatments as well as prevention of relapse play a critical role in the reduction of disease reservoirs, and form a vital part of disease control. In addition, co-infection of kala-azar and HIV is a growing problem and renders treatment more difficult for both diseases.

AfriCoLeish brings together six organizations from Europe and East Africa with vast experience in R&D and treatment of HIV and kala-azar, namely the Drugs for Neglected Diseases initiative (DNDi); the Institute of Tropical Medicine (ITM) in Antwerp; the London School of Hygiene & Tropical Medicine; Medecins Sans Frontieres (MSF, The Netherlands); the Institute of Endemic Diseases, University of Khartoum (IEND), Sudan; and the University of Gondar (UoG), Ethiopia.


New guide to improve procurement performance

The USAID Deliver Project has published three new documents that can help supply chain programme managers understand and track key performance indicators for the procurement process. The Procurement Performance Indicators Guide Using Procurement Performance Indicators to Strengthen the Procurement Process for Public Health Commodities describes suggested key indicators that can be helpful in tracking various aspects of a procurement system.

The guide is intended for procurement managers at ministries of health and central medical stores who are responsible for procuring public health commodities. It is complemented by the Procurement Performance Indicators Dashboard, a Microsoft Excel spreadsheet that captures performance data and graphically summarizes results for each indicator in a dashboard format.

ATC/DDD Classification

ATC/DDD Classification (Temporary)

The following anatomical therapeutic codes (ATC), defined daily doses (DDD) and alterations were considered by the WHO International Working Group for Drug Statistics Methodology at its meeting in March 2013. Comments or objections to the decisions should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology at whocc@fhi.no. The new ATC codes, DDDs and alterations will then be considered final and be included in the January 2014 version of the ATC/DDD index. The inclusion of a substance in the lists does not imply any recommendation for use in medicine or pharmacy.

New ATC 5th level codes:

<table>
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<tr>
<th>ATC level</th>
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<th>ATC code</th>
</tr>
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<td></td>
<td>afamelanotide</td>
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<tr>
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</tr>
<tr>
<td></td>
<td>brimonidine</td>
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<tr>
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<td>calcium citrate</td>
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</tr>
<tr>
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<td>delamanid</td>
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<tr>
<td></td>
<td>dienogest and ethinylestradiol</td>
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<td></td>
<td>empagliflozin</td>
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</tr>
<tr>
<td></td>
<td>encephalitis, Japanese, live attenuated</td>
<td>J07BA03</td>
</tr>
<tr>
<td></td>
<td>formoterol and fluticasone</td>
<td>R03AK11</td>
</tr>
<tr>
<td></td>
<td>insulin degludec</td>
<td>A10AE06</td>
</tr>
<tr>
<td></td>
<td>insulin degludec and insulin aspart</td>
<td>A10AD05</td>
</tr>
<tr>
<td></td>
<td>lamivudine, tenofovir disoproxil and efavirenz</td>
<td>J05AR11</td>
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<td>macitentan</td>
<td>C02KX04</td>
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<td>metformin and dapagliflozin</td>
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<td>N07BB05</td>
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<td>A06AH03</td>
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### ATC level

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#### Change of ATC code:

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#### Change of ATC level names:

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<td>cannabinoids</td>
<td>N02BG10</td>
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<tr>
<td>Insulins and analogues for injection,</td>
<td>Insulins and analogues for injection,</td>
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</tr>
<tr>
<td>intermediate-acting combined with fast-acting</td>
<td>intermediate- or long-</td>
<td>A10AD</td>
</tr>
<tr>
<td>Acting combined with fast-acting</td>
<td>long-acting combined with fast-acting</td>
<td>G02AX</td>
</tr>
<tr>
<td>Other oxytocics</td>
<td>Other uterotonics</td>
<td>G03XB</td>
</tr>
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<td>Antiprogestogens</td>
<td>Progesterone receptor modulators</td>
<td>G02A</td>
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<td>Oxytocics</td>
<td>Uterotonic</td>
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#### New DDDs:

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<td>Inh powder</td>
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<tr>
<td>86</td>
<td>mg</td>
<td>O</td>
<td>J04AK05</td>
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<tr>
<td>1.2</td>
<td>g</td>
<td>P</td>
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<td>10</td>
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<td>5</td>
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* refers to aclidinium, delivered dose
** refers to glycopyrronium, delivered dose
ATC/DDD Classification

ATC/DDD Classification (Final)

The following anatomical therapeutic codes (ATC), defined daily doses (DDD) and alterations were agreed by the WHO International Working Group for Drug Statistics Methodology at its meeting in October 2012. These ATC codes, DDDs and alterations are considered as final and will be included in the January 2014 version of the ATC/DDD index. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted at whocc@fhi.no The inclusion of a substance in the lists does not imply any recommendation for use in medicine or pharmacy.

New ATC 5th level codes:

<table>
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<tr>
<th>ATC level</th>
<th>INN/Common name</th>
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<td>ulipristal</td>
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<td>bedaquiline</td>
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<tr>
<td></td>
<td>teriflunomide</td>
<td>L04AA31</td>
</tr>
<tr>
<td></td>
<td>phenibut</td>
<td>N06BX19</td>
</tr>
</tbody>
</table>

Continued/
Mebicar N06BX21
Ipidacrine N06DA05
Dimethyl fumarate N07XX09
Laquinimod N07XX10
Olodaterol R03AC19
Vilanterol and fluticasone furoate R03AK10
Vilanterol and umeclidinium bromide R03AL03
Indacaterol and glycopyrronium bromide R03AL04
Cineole R05CA13
Sequifenadine R06AX32
Mercaptamine S01XA21
Technetium (99mTc) etarfolatide V09IA08
Radium (223Ra) dichloride V10XX03

New ATC level codes (other than 5th levels):
ACE inhibitors, other combinations C09BX
Adrenergics in combination with anticholinergics R03AL 1

Change of ATC codes:

<table>
<thead>
<tr>
<th>Level name</th>
<th>Previous ATC code</th>
<th>New ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen, human</td>
<td>B02BC10</td>
<td>B02BC30</td>
</tr>
<tr>
<td>Ferric oxide polymaltose complexes</td>
<td>B03AC01</td>
<td>B03AC03</td>
</tr>
<tr>
<td>Saccharated iron oxide</td>
<td>B03AC02</td>
<td>B03AC03</td>
</tr>
<tr>
<td>Iron-sorbitol-citric acid complex</td>
<td>B03AC03</td>
<td>B03AC03</td>
</tr>
<tr>
<td>Ferric sorbitol gluconic acid complex</td>
<td>B03AC05</td>
<td>B03AC03</td>
</tr>
<tr>
<td>Ferric oxide dextran complexes</td>
<td>B03AC06</td>
<td>B03AC03</td>
</tr>
<tr>
<td>Ferric sodium gluconate complex</td>
<td>B03AC07</td>
<td>B03AC03</td>
</tr>
</tbody>
</table>

Change of ATC code and/or ATC level name:

<table>
<thead>
<tr>
<th>Previous</th>
<th>New</th>
</tr>
</thead>
<tbody>
<tr>
<td>R03AK03 fenoterol and other drugs for obstructive airway diseases</td>
<td>R03AL01 fenoterol and ipatropium bromide</td>
</tr>
<tr>
<td>R03AK04 4 salbutamol and other drugs for obstructive airway diseases</td>
<td>R03AK04 salbutamol and sodium cromoglicate</td>
</tr>
<tr>
<td>R03AL02 salbutamol and ipatropium bromide</td>
<td>R03AK07 formoterol and budesonide</td>
</tr>
<tr>
<td>R03AK08 formoterol and beclometasone</td>
<td>R03AK09 formoterol and mometasone</td>
</tr>
</tbody>
</table>
Change of ATC level names:

<table>
<thead>
<tr>
<th>Previous</th>
<th>New</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenergics and other drugs for</td>
<td>Adrenergics in combination</td>
<td>R03AK</td>
</tr>
<tr>
<td>obstructive airway diseases</td>
<td>with corticosteroids or other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>drugs, excl. anticholinergics</td>
<td></td>
</tr>
<tr>
<td>reproterol and other drugs for</td>
<td>reproterol and sodium</td>
<td>R03AK05</td>
</tr>
<tr>
<td>obstructive airway diseases</td>
<td>cromoglicate</td>
<td></td>
</tr>
<tr>
<td>salmeterol and other drugs for</td>
<td>salmeterol and fluticasone</td>
<td>R03AK06</td>
</tr>
<tr>
<td>obstructive airway diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron trivalent, parenteral preparations</td>
<td>Iron, parenteral preparations</td>
<td>B03AC</td>
</tr>
<tr>
<td>thyrotropin</td>
<td>thyrotropin alfa</td>
<td>H01AB01</td>
</tr>
</tbody>
</table>

1 Split of ATC 4th level R03AK, separate 4th level for combinations with anticholinergics.
2 Combinations previously classified in B02BC10 should be altered to B02BC30 combinations (existing code).
3 ATC 5th levels deleted, all products classified on the 4th level only (B03AC Iron, parenteral preparations).
4 Separate ATC 5th levels for the various combinations (split of code). New ATC 4th level (R03AL) for combinations with anticholinergics.

New DDDs:

<table>
<thead>
<tr>
<th>DDD</th>
<th>unit</th>
<th>Adm.R</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>aclidinium bromide*</td>
<td>0.644</td>
<td>mg</td>
<td>Inhal powder</td>
</tr>
<tr>
<td>gemigliptin</td>
<td>50</td>
<td>mg</td>
<td>O</td>
</tr>
<tr>
<td>colecalciferol</td>
<td>20</td>
<td>mcg</td>
<td>O</td>
</tr>
<tr>
<td>thyrotropin alfa</td>
<td>0.9</td>
<td>mg</td>
<td>P</td>
</tr>
<tr>
<td>pasireotide</td>
<td>1.2</td>
<td>mg</td>
<td>P</td>
</tr>
<tr>
<td>ivacaftor</td>
<td>0.3</td>
<td>g</td>
<td>O</td>
</tr>
</tbody>
</table>